New Orleans Medical
and
Surgical Journal

Vol. 99 FEBRUARY, 1947 No. 8

SADDLE BLOCK ANESTHESIA*
ITS APPLICATION TO OBSTETRICS

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Saddle block is a term used to designate a form of low spinal anesthesia confined to the perineal area. It differs from low spinal anesthesia induced in the ordinary methods in having a greater degree of controllability. Exact localization of anesthesia in the sacral segments with comparatively small doses of local anesthetic drugs may be obtained. The authors have employed the technic for rectal, urologic and gynecologic surgery for some time. The same extent of anesthesia obtained with caudal block is obtained with saddle block in a simpler, safer and more precise manner. By using longer lasting drugs such as pontocaine or nupercaine anesthesia and analgesia lasting two and three hours, respectively, may be obtained by a single injection. The recent popularization of caudal anesthesia for obstetrics by the continuous technic suggested to the authors that saddle block could be used instead and might be more desirable.

On the whole, spinal anesthesia has not been popular in obstetrics. One of the drawbacks has been that procaine has been considered the drug of choice. Although procaine is excellent for spinal anesthesia, its duration of action usually averages an hour. The injection must be repeated frequently; otherwise the drug can only be used for anesthesia for the delivery. The longer lasting drugs allow its use for analgesia during labor as well as for the manipulations of delivery. In view of the excellent results obtained with saddle block in surgery, there did not appear to be any reason why its use could not be extended to obstetrics. This is a report of our experiences in extending the use of the block in obstetrics. Nupercaine and pontocaine have been employed to provide the desired longer duration.

TECHNIC

The materials for performing a saddle block are the same as those used in spinal anesthesia. A wheal needle, a 20 gauge short bevel spinal needle and a 2 c.c. syringe are the necessary items. Glucose (10 per cent) in physiologic saline or distilled water, a 1/200 solution of nupercaine and 1 per cent procaine for infiltration are the necessary solutions and drugs. If pontocaine is desired the 1 per cent solution is employed.

Nupercaine, 0.5 c.c. of 1/200 solution is thoroughly mixed with 0.5 c.c. of 10 per cent glucose solution and drawn into one of the 2 c.c. syringes. The solution thus prepared contains 2.5 mgm. of nupercaine. Five milligrams of pontocaine must be drawn and mixed with the glucose if this drug is employed. No spinal fluid is necessary in the preparation of the fluid in either case. The patient is placed in the sitting position in the center of the operating or delivery table, or at the edge of the bed with

*Read before the sixty-sixth annual meeting of the Louisiana State Medical Society, Alexandria, May 6-8, 1946.

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legs dangling over the side. The puncture is simplified if the patient leans forward with her arms folded across the chest and her shoulders are supported by an assistant. An intradermal wheal is raised at the fourth lumbar interspace and the interspinuous tissues are infiltrated with 1 per cent procaine. The third interspace may be employed if the fourth is not accessible. There is little difference in the level of anesthesia obtained in either case. The syringe containing the solution is attached to the needle and aspiration is attempted to insure a free flow of spinal fluid. Not more than 0.1 c.c. of spinal fluid should be withdrawn into the syringe, otherwise dilution of the solution which causes spreading of the drug beyond the desired spinal segments occurs. The needle should be readjusted until a satisfactory flow of spinal fluid is obtained if it does not flow freely. Failures in spinal anesthesia can usually be ascribed to unsatisfactory lumbar puncture. It is advisable to prepare the solution in advance of the lumbar puncture to avert failures due to dislodgment of the needle by sudden unexpected movements of the patient. The solution is injected as rapidly as gentle pressure upon the plunger of the syringe permits—usually less than two seconds. The patient is then allowed to remain in the upright sitting position for thirty seconds after completion of the injection after which time she is placed in the recumbent position. The head is elevated on a pillow in order that the neck may be flexed. The solution should not be introduced during a uterine contraction because the spinal fluid pressure and currents established in the subarachnoid space force the drug into the thoracic region. The table may be flat or placed in a reversed Trendelenburg position at an angle of approximately 5°. The glucose causes the solution to be hyperbaric or heavier than spinal fluid. The drug is therefore carried downward to the tip of the dural sac. The anesthesia in these segments will be intense and well localized. It is well known that sensory and autonomic fibers of a mixed nerve are more sensitive to the effects of a given concentration of a local anesthetic drug than the motor. If the patient is promptly returned to the recumbent position a given dose of drug becomes distributed over more segments of the cord than if she remains sitting for some time. In either case, the sacral segments are exposed to a more concentrated solution of drug than the lumbar and both the motor and sensory fibers of these segments are affected. The perineal area is more completely anesthetized and relaxed. When the patient sits up sixty or more seconds there is no sensory anesthesia or motor paralysis in the legs and thighs. If the patient sits up 30 seconds, the lumbar segments are exposed to a weak concentration of solution of the drug. Sensory anesthesia of the legs and thighs with little or no paralysis of the leg and thigh muscle is obtained. In most cases the analgesia over the thigh gradually merges into an area of hypalgesia over the lower abdomen. This distribution is desirable for obstetrics because it also affects the sensory fibers of the uterus and cervix. The sensory fibers to the cervix and lower uterine segments are derived from the sacral and lower lumbar spinal nerves; those of the upper part and the fundus from the upper lumbar and twelfth thoracic segments. The motor innervation is still a matter of question. It is believed that the motor fibers are derived from the thoracic segments. Consequently, there is no diminution in the number or force of the contractions because the drug does not extend to this level. Pain from contractions disappears, but labor continues.

METHOD OF STUDY

The technic in this study was limited exclusively to normal primipara or multipara. Patients presenting any systemic abnormalities or obstetric complications were excluded. The block was performed after the inception of the first stage of labor—usually when the contractions appeared at three or four minute intervals and the cervix was 5-6 cm. dilated or approximately 80 per cent effaced. Sedatives were purposely omitted in order to evaluate the effects of the block alone properly. Blood pressure and pulse rate were recorded at three or four

minute intervals, shortly after induction of analgesia, and at 10 to 15 minute intervals after the first half hour. The anesthetist remained in constant attendance closely observing the frequency and intensity of contractions, fetal heart tones, progress of labor, respiration, and other reactions of the patient. Apparatus for the administration of oxygen or artificial respiration were held in readiness as is the usual procedure in all cases of spinal anesthesia. If repetition of the block was necessary, the injection was repeated in exactly the same manner as the previous injection as soon as analgesia began to disapppear.

RESULTS

Satisfactory analgesia during labor and anesthesia at the time of delivery were obtained in the majority of cases. Nupercaine was used in 88 per cent of the cases. Pontocaine was chosen when less than two hours' analgesia seemed indicated. Anesthesia became established within two to five minutes and lasted an average of three hours with both drugs. The onset of anesthesia, when nupercaine or pontocaine are mixed with glucose, may require four or five minutes. In some cases using nupercaine, analgesia lasted as long as five hours. The average, however, was three hours with nupercaine and two hours with pontocaine. Seventy-seven per cent of the subjects experienced complete pain relief. Fifteen per cent complained of pain in the upper abdomen during the period of traction of the forceps. The pain was described as a dull ache in the epigastrium or along the back in the lumbar region. Inhalation of analgesic concentrations of nitrous oxide was sufficient to relieve this discomfort. Pain in the perineum during repair of the episiotomy was absent. Seven per cent complained of pain in the perineum or back or were not relieved of the pain from the uterine contractions. Failure to obtain satisfactory analgesia was ascribed to errors in technic. It is imperative that timing and measurements of volumes of solutions be precise if a successful block is to be obtained. The block was repeated after 15 or 20 minutes. Satisfactory analgesia was obtained the second time in all these. There is no objection to or danger in immediately reattempting the block in the event of failure because the doses employed are small.

The patients were comfortable and cooperative throughout the labor and delivery. Patients in pain or who were not cooperative before the block was performed, immediately became so. Patients were able to bear down when so instructed and aid in the delivery since the abdominal muscles were not paralyzed. The absence of paralysis in the legs and thighs allowed the patient to move about in bed and shift to desired positions. In some patients a mild paresis of the thigh and leg muscles was present but it did not interfere with motion, although it did limit it to certain extent. The analgesia in the legs and thighs was a desired feature because it alleviated discomfort when the lithotomy position was instituted during the delivery. Low forceps were used in 68 per cent of the patients. A single injection was sufficient in 80 per cent of all cases. In 30 per cent, labor outlasted analgesia and second or third injections were required. The shortest time from the institution of analgesia until delivery was 15 minutes; the longest 11 hours, 51 minutes. The injection was repeated twice in the latter case. The third stage of labor was not remarkably different from cases delivered with other types of analgesia or anesthesia. Postpartum hemorrhage was not encountered; excessive bleeding was no problem. The babies cried spontaneously and required no rescuscitation.

Nausea was present in 10 per cent of the patients; vomiting in 8 per cent. Nausea was most prevalent among patients who were given food or fluids during labor. This occurred early in the series and was a source of concern until the cause was recognized. It is advisable to restrict fluids and food during labor to avoid this complication. A reduction in blood pressure averaging 10 mm. mercury systolic was noted in 50 per cent of the cases. The lowering was attributed to removal of psychic effects or to the pain relief. A momentary systolic drop, sometimes as low as 80 mm.

mercury occurred shortly after completion of the injection. Recovery was, however, spontaneous and required no therapy other than deep breathing.

Hypotension with bradycardia is characteristic of spinal anesthesia, particularly when the block is extensive. However, it is unusual during saddle block. In this series it was absent in all but five cases. In these, the blood pressure fell below 80 systolic and continued at this level for some time. Ephedrine 15 mg. intravenously, restored the blood pressure to the preanesthetic level. The number of spinal segments affected in saddle block is few. Motor anesthesia is confined to a few small muscles. Physiologic changes, therefore, are minimal and compare in no way with those encountered in the usual type of spinal anesthesia in which numerous spinal segments are anesthetized. Respiratory embarrassment was not encountered in any case. Although hysterographic and other studies of the effects upon labor were not attempted, it was obvious at the outset that labor was retarded if the block was performed before strong regular contractions were present and the cervix was dilated. Likewise the impression was gained that the incidence of delivery by forceps was increased. If the block extends too high (analgesia of the thoracic nerves) labor is retarded.

Post spinal headache, backache, urinary retention, distention, ileus, meningismus, palsies or other complications were not encountered in the series.

DISCUSSION

Obviously, 156 cases is not a sufficient number to prove the merits or demerits of this or any other method of analgesia or anesthesia. However, the applicability of saddle spinal block to obstetrics is established. One must bear in mind that the usual objections, hazards, and complications of spinal anesthesia in a series as small as this is of no significance. It must be emphasized that these were normal cases, free from all complications and that the applicability of this method of analgesia to other than uncomplicated obstetrical cases requires further study.

Saddle spinal offers certain advantages over the continuous caudal block. The uncertainty of locating the caudal canal, the presence of an indwelling needle on catheter, the hazards of improper placement of the needle, the repeated use of relatively large volumes of local anesthetic solutions, the uncertainty of distribution of anesthesia are eliminated in this technic.

SUMMARY

Saddle block anesthesia is a form of low spinal anesthesia confined to the perineal area. A technic is described for prolonged analgesia using the longer lasting drugs—nupercaine and pontocaine. The block was used in 156 normal deliveries with satisfactory results. The applicability of this method of anesthesia and analgesia to obstetrics is demonstrated by its success in this series. The method is recommended when spinal anesthesia is desired or indicated in obstetrics. It possesses the advantage of certainty and simplicity over the continuous caudal technic.

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THE PREVENTION OF Rh ISOIMMUNIZATION DUE TO BLOOD TRANSFUSION

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In no phase of Rh investigation has more rapid advance taken place than in the development of procedures for detecting the various Rh antibodies, which are, of course, the actual serologic proofs of isoimmunization. Thanks to the efforts of a small number of investigators, and their associates, serologic laboratories today have at their command a number of excellent tests for the detection and identification of Rh antibodies. I have found these procedures to be most useful when employed in parallel. They include the agglutination and absorption tests of Levine[1, 2], the blocking and so-called conglutination tests of Wiener[3, 4],

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Diamond's slide agglutination procedure[5] and various modifications of each.

While the tools available for demonstrating Rh isoimmunization have thus increased both in numbers and accuracy, we are still largely without power to permanently inhibit or neutralize the antibodies once they have been proliferated. As is well known, the Rh complex is highly antigenic in some humans and Rh—individuals may become sensitized or isoimmunized following the entrance of Rh+blood into their circulations, either by transfusion, pregnancy, or both.

However, it is unusual indeed for an Rh—person to become sensitized following a single exposure to Rh+blood. Only about 15 per cent of the white race are Rh—and of this minority group not more than 5 per cent seem capable of being sensitized even following several exposures to the antigen (Rh+blood).[6] Most unfortunately, there is no method known for indicating which of the Rh—individuals will become sensitized and form antibodies if exposed to Rh+ blood. When one considers again that there is still no way yet known for safely deimmunizing sensitized persons, the vital importance of preventing isoimmunization becomes apparent. As far as pregnancy is concerned, it has been suggested that Rh typing should become a part of premartial blood tests and that Rh+men should be forbidden to marry Rh—women. This idea is ridiculous in light of the statistics on sensitization already mentioned and certainly unthoughtful of basic human rights.

Now, when we examine the sensitization problem from the transfusion approach, we are in better position to accomplish a useful end. The repeated transfusion of Rh+blood into Rh— recipients very infrequently produces isoimmunization. However, it does occur at times in both sexes although producing a less intense degree of antibody formation than Rh+pregnancies in Rh— mothers. The relationship between maternal Rh antibodies and the syndrome "hemolytic disease of the newborn" is well established and requires but passing mention at this time.*

While this syndrome, in one stage or another, is seen only in about one in 250 deliveries[7] more than 90 per cent of the time it is the result of the now classical relationship of Rh—mother and Rh+father and baby.[8] In these cases the maternal antibodies attack the fetal erythrocytes and set in motion a chain of patho-physiological events leading to the development of the hemolytic syndrome. Succeeding Rh+pregnancies are usually affected more severely.

Practically the only weapon we have at present for preventing Rh isoimmunization is the routine Rh typing of all patients who are to receive transfusions, ensuring that Rh—patients will receive Rh—blood. It is most essential that this routine test be done in the case of female patients, first because of the two routes of sensitization open via transfusion and pregnancy and secondly because in the case of women of childbearing age or younger, there are future offspring to consider. Indeed, from the viewpoint of possible sensitization a blood transfusion in a woman should be regarded as equivalent to a pregnancy. The routine typing must also include little girls and female infants. As will be shown later, the transfusion of Rh+blood into an Rh—girl can produce a sensitization which will persist for years and which will flare up on subsequent exposures to the antigen, leading to hemolytic transfusion reactions or to hemolytic disease of the newborn.

At this point it is in order to refer to a recent report published by Levine and Waller[9] concerning the incidence of erythroblastosis fetalis in first born children. This extensive study showed a higher degree of incidence and severity of erythroblastosis in the Rh+first born children of Rh— mothers where the mothers had a history of having received one or more blood trans-

(*) The term "hemolytic disease of the newborn" is used to include erythroblastosis fetalis, icterus gravis neonatorum and hydrops fetalis, all three of which clinical entities stem from the same basic cause—extensive blood destruction in the fetus with excessive compensatory erythropoiesis.

fusions from a few months to several years before the first pregnancy. Significantly, in a group of Rh—mothers of affected Rh+ first born infants, although the mothers had negative transfusion histories, it was not possible to rule out completely the intramuscular injection of blood in these mothers during their own infancy. In this connection it must be stressed that the intramuscular injection of blood will sensitize a susceptible Rh—person practically as well as the intravenous injection.

In the case of older women the Rh type obviously should be determined, since this group may have been sensitized years before by transfusions or pregnancy and may suffer severe or even fatal reactions to otherwise compatible Rh+blood.

Certainly the ideal situation must and will some day be the routine Rh typing of all patients who are to receive transfusions, with Rh—blood only being given to the Rh—patients. Modern blood banks are struggling toward this goal but are hampered at present by the frequent difficulty of obtaining adequate supplies of reliable Rh testing sera and by the problem of maintaining an abundant supply of Rh—donor blood. However, as more and more Rh cases are studied, the serum situation is improving, and since most banks Rh type all their donors the number of known Rh—people in almost every community will increase.

Even in the most efficiently operated blood banks the demand for Rh—blood at times exceeds the supply. Since we feel that it is more essential that Rh—females receive Rh—blood, we do not routinely Rh type male patients. The procedure is done on men only when indicated by a history of repeated transfusions or of one or more unfavorable reactions to transfusion. In such cases the patient's serum is tested for Rh antibodies and if these are present, he is given Rh—blood. In my experience this policy has proven to be satisfactory in operation because it frees quantities of Rh—blood for the more urgent need of female patients. Further, in the space of the past three and one-half years, during the course of several thousand Rh examinations and blood transfusions, I have encountered but three cases in which the repeated administration of Rh+blood to Rh—males induced the formation of antibodies. In each case the antibodies were detected before any severe reaction occurred and subsequent transfusions were with Rh—blood.

As has been stated, once Rh isoimmunization has been established, there is nothing at present to be done to correct the situation. This presents no great obstacle to transfusion therapy other than obtaining suitable Rh—bloods for Rh—patients. Since Rh follows a definite genetic pattern within any family, we have at times been successful in obtaining additional supplies of Rh—blood by Rh typing close blood relatives of the patient.

Even though only a small percentage of Rh—people ever become sensitized, it is quite apparent that every effort must be made to prevent accidental sensitizations which might result from the transfusion of Rh+blood to Rh—recipients. Only by accurately Rh typing all patients who are to receive blood, can we hope to avoid instances of inadvertent isoimmunization with its sequelae of hemolytic reactions and/or complications of pregnancy. When one analyzes the Rh problem in relation to pregnancy, many far reaching ramifications may be perceived, for here we are dealing not only with the patient herself but must weigh the potential effect of maternal antibodies which may be induced by future pregnancies.

In selecting cases to include in this report, I have deliberately chosen those which can be held up as "horrible examples" of what may happen if a young female patient is given blood without regard to her Rh type. It must be said, however, that in two of the cases, the original transfusions were given some years before the discovery of the Rh Factor, while in one case, knowledge of Rh was very much in its infancy and no typing sera were available, even if we had realized that we should have Rh typed the patient.

CASE NO. 1

In 1936, the patient, a girl 12 years old, was admitted to another hospital with a diagnosis of streptococcic septicemia. While there she received a 500 c.c. indirect blood transfusion from her uncle, with no untoward reaction. No other blood was given and recovery was uneventful.

In August, 1944, now 21 years old and married, the patient was delivered of a full term male infant exhibiting marked jaundice and erythroblastotic anemia. Rh types and blood groups as determined by the writer were as follows: patient Rh — Group A; husband Rh+ Group A; infant Rh + Group A. In spite of a transfusion of 75 c.c. of compatible Rh — blood, the baby expired in about 48 hours. The original diagnosis of hemolytic disease of the newborn was confirmed by postmortem findings, most of the liver and a large portion of the spleen being replaced with the characteristic, accessory erythropoietic tissue.

The patient's serum was tested for anti-Rh agglutininins by the saline-cell suspension method. Results were negative. Undoubtedly blocking antibody would have been found at this time, had that test been known.

In February, 1945, the patient was referred back to the writer and in reviewing her history, the fact of the transfusion more than eight years previously was elicited. We were able to obtain a blood sample from the relative who had been the donor and found him to be Group A Rh +. The patient's serum was still negative for anti-Rh agglutinins but rather strong blocking antibody was found, in a titer of 1:8. The writer's serologic findings in this case were confirmed by Dr. Philip Levine who also very kindly determined the Rh genotype of the husband, establishing it as homozygous (Rh-Rh). This latter point made the prognosis for future pregnancies very poor. Since the couple wished to attempt another pregnancy, however, they were advised to wait for at least two years, not with the idea of causing a loss of sensitivity in the wife, but rather to permit the actual antibodies to disappear from her circulation.

Unfortunately, the patient became pregnant again within a short time. She was admitted to the hospital on October 2, 1945, and two days later was delivered of a six and a half month, macerated fetus which had been dead about six weeks. The patient had not felt life since the second week of the fifth month. Because the fetus was in a considerable state of decomposition, its blood being hemolyzed, the Rh type could not be determined. Undoubtedly it was actually Rh + since examination of the mother's serum showed the presence of very strong Rh blocking antibodies as well as a positive test with Rh + control cells suspended in normal serum. The titer of the blocking antibody increased from 1:4 to 1:64 during the fourth month of the pregnancy and remained at the higher level for more than two months after delivery of the dead fetus.

DISCUSSION

What is the prognosis for future pregnancies? As a serologist I am convinced that this husband and wife, because of their Rh relationship, can never have a normal baby, or, indeed, a living one. Unless or until a means of de-immunization is worked out this woman can have no living children by her husband. Thus one may contemplate the end result of a chain of patho-physiolgic events innocently started with a blood transfusion nearly nine years before the patient's first pregnancy. (Note—Certain aspects of this case have been previously discussed elsewhere.[10])

CASE NO. 2

During the winter of 1939-40 this patient, a young lady then 20 years old, was admitted to the hospital for treatment of a ruptured appendix. During her stay she was given a total of eight group compatible blood transfusions, with no untoward reactions. Subsequently she married and in August, 1943, gave birth to a full term stillborn, macerated fetus. (Apparently no postmortem examination was done, as records were not available.)

In July, 1945, the patient was referred to me for Rh examination. She was then about three and a half months pregnant (grav. ii), the E. D. C. being January 29, 1946, and was found to be group B Rh—. Her serum contained weak anti-Rh agglutinins and moderately strong blocking antibody. Just how much of this was residual from her first pregnancy was difficult to decide. The husband was found to be Group O Rh +. These findings were confirmed by Dr. Levine, but the genotype of the husband could not be definitely established.

Because of the patient's history it was decided to check her serum at four to five week intervals. Relatively early the blocking antibody titer reached 1:128 and with one exception persisted at that level for all subsequent tests. The anti-Rh agglutinins increased slowly in strength during the course of the pregnancy while the slide agglutinin test increased noticeably in the latter part of the seventh month.

In view of the serologic findings the obstetrician decided to perform a cesarean section approximately one month before term, in an effort to remove the baby from its serologically harmful environment. The operation was performed uneventfully on December 29 and a six and a half pound, viable male infant delivered. The baby was not jaundiced. About 50 c.c. of group compatible Rh — blood were given in an umbilical vein immediately after birth. By the morning of December 30 the baby had be-

come deeply jaundiced and the blood count had dropped to 3.5 million, with 60 per cent hemoglobin. The baby, being group B Rh+, was given a transfusion of 75 c.c. of Group B Rh— blood, with the blood count increasing to 4.6 million, and hemoglobin to 75 per cent. No erythroblasts were present in blood smears. However, there was marked hepatic enlargment and slight enlargement of the spleen. In spite of a third transfusion of 90 c.c. Group B Rh— blood, the baby failed rapidly and expired on the morning of December 31, about six hours after developing a pulmonary hemorrhage. One week following the delivery, the mother's serum showed the continued presence of strong Rh antibodies.

DISCUSSION

In this case one is again faced with the problem of giving the husband and wife a prognosis for future pregnancies. Because the husband's Rh genotype is in doubt, so that he might be heterozygous (Rhrh) and thereby capable of fathering an Rh—child, the prognosis is somewhat better than in the preceding case. However, even if one actually knew the father to be heterozygous, the prognosis could go no further actually than to state that while an Rh—child is possible in this couple and would not cause the mother to proliferate antibodies, there is no way of determining if the next child would be Rh+ or Rh—.

We were able to test the bloods of four of the people who donated blood to the patient in 1939-'40 and found one of them to be Group B Rh+ and three of them to be Group B Rh—. (One of the Rh—donors was the patient's brother.)

In 1939, when this girl was first a patient, if the knowledge of Rh had been comparable to its present development there is every reason to believe that her first child would have survived, for had we known of the importance of Rh typing young women, this patient would have received only Rh—blood and thus would not have been sensitized to the Rh factor prior to her first pregnancy.

CASE NO. 3

In December, 1939, the patient, then a girl 16 years old, was admitted to the hospital for treatment of first and second degree burns of the upper extremities. On December 31 she received, uneventfully, 380 c.c. of group compatible blood. Another transfusion, from a different donor, was given on January 2, 1940, with no untoward reaction.

On May 31, 1946, the patient, together with her husband and two year old daughter, was referred to the writer for Rh examination. The patient was found to be Group O, Rh—; the husband Group A, Rh+; and the little girl Group O, Rh+. Testing of the patient's serum revealed no definite evidence of anti-Rh antibodies, although there seemed to be a faint trace of blocking antibody present. No especial significance was attached to this since the patient was only six weeks pregnant at the time of her first visit to the laboratory. She was requested to return in about four weeks' time. On July 7 her blood showed definite blocking antibody, with a titer of 1:8 as well as other Rh antibodies in weaker strength. The question immediately arises as to when the patient was first sensitized to the Rh factor. One of the donors who gave her blood in 1939-40 was recently typed and found to be Rh+ and group compatible. Thus one (or perhaps both) of the transfusions could have initiated the isoimmunization, while her first pregnancy (with Rh+ baby) could have intensified it. Now she is pregnant again and it is predicted that the fetus is Rh+. There is no other explanation for the presence of Rh antibodies so early in the pregnancy except, perhaps, that they are residual from the first pregnancy. If they were present then they were of insufficient strength to injure the first child. At any rate, the patient is again pregnant, has antibodies and the prognosis is not good because the antibodies are of the blocking variety. Perhaps it is a moot question as to just how much the blood transfusions of six years ago contributed to the patient's present immunologic status. Most probably they initiated the sensitivity which has progressed to such a level that now in the third month of the second pregnancy the patient has sufficient blocking antibody present in her serum to cast grave doubts on the survival of the fetus.

DISCUSSION

It will be noted in all three of the above cases that the Rh—recipient was given Rh+ blood quite accidentally because in two cases the procedures were carried out prior to the discovery of the Rh complex and in the other not enough was known of the subject at the time. It is of course quite evident that such episodes, involving the administration of Rh+blood to an Rh—recipient, can (and still do) occur in spite of the tremendous amount of working information that we now have on the Rh factor. Such unfortunate occurrences may result either from failure to Rh type the blood of the patient or may lie in er-

roneous typing of the patient and/or donor. To my mind, failure to routinely Rh type transfusion patients (most especially females) is a greater sin than to mistype a blood once in a while. The latter will happen in the best of laboratories and the larger the service and the more personnel concerned, the more likely are such mistakes to occur. But, the very least that can be done is to try to establish accurate methods of Rh typing and then use them routinely. If a blood is occasionally Rh mistyped currently available procedures usually serve to detect the error before the blood is administered to the patient. Recently the writer had occasion to examine the blood of a patient concerned in just such an episode. The patient is a 58 year old white male who has cirrhosis of the liver, and in past months has been receiving frequent transfusions. Originally his blood was classified as Group A, Rh+, and in the course of several weeks he uneventfully received some eight pints of Rh +blood. A recheck was made on his Rh type and it was found actually to be Rh—. Since then he has received three pints of Rh—blood with no untoward reactions. A sample of his blood was sent to this laboratory to be examined for irregular agglutinins, particularly autoagglutinins. Actually no such agglutinins were present, but the serum did contain very potent anti-Rh agglutinins. The patient was found to be Group A_1 Rh—.

This case is mentioned at some length because it is an example of Rh sensitization in a male patient as a result of repeated transfusions of Rh+blood and because it characteristically illustrates that several pints of positive blood are usually required to sensitize an Rh—male. It should be noted that a single pregnancy often has more immunizing power than a large number of transfusions alone.

Cases such as those presented herein are admittedly rare, even as Rh isoimmunization itself is infrequent. Yet we cannot afford to overlook the fact that transfusion of Rh+blood at any age may produce a sensitivity in an Rh—person which will persist for years or perhaps for life, a potentially evil thing lurking in the reticulo-endothelial system and ready, as soon as the antigen (Rh+blood) is reintroduced into the body, to injure the patient, or, in the case of a woman, even destroy her children before they are born. Again, one must admit that such cases are statistically rare, compared with other medical conditions, but they are very real and poignant tragedies to the husbands and wives concerned. These cases can be prevented — they must be prevented.

SUPPLEMENT

Some additional remarks on this phase of the Rh problem are indicated by new information becoming available since the foregoing paper was written.

For one thing, we must abandon the idea that only about 5 per cent of Rh—people are capable of isoimmunization. Diamond[11] has shown that a more accurate estimate is nearer 50 per cent, or some ten times greater. It can be appreciated, therefore, that the potential danger inherent in disregarding the Rh factor in transfusions to females is proportionately greater than had been assumed.

Regarding male patients, I have had no occasion to change my earlier views, although Diamond's figure applies equally to them. As long as *ample* supplies of Rh— blood continue difficult to procure we do not propose routinely to Rh type males except, as stated above, when this procedure is indicated by the patient's transfusion history. It must be remembered that not every person in the 15 per cent Rh— segment of the general population is suitable as a donor, as this group includes children, old people and sick individuals as well as the Rh— patients requiring transfusion. Very probably not more than 5 per cent of the Rh— people in the average community are available as donors at any one time.

Another early concept that must be altered is that the Rh factor is confined to the erythrocytes and is not secreted in various body fluids as are the A and B factors.

In enlarging on an earlier report[12] Witebsky[13] recently commented on finding Rh substance in the amniotic fluid of some Rh+ fetuses and in the saliva and gastric juice of a few other Rh+ individuals. This may serve to explain some of the occasional normal Rh+ babies born to Rh— mothers who have exhibited antibodies during pregnancy. Further it brings nearer the realm of probability a preparation suitable for the *in vivo* neutralization of Rh antibodies. The problem of antigenicity of such a substance has been attacked by Calvin[14] and others.

Even if we had such an agent it would still behoove us to continue our efforts to prevent such cases as have been reported above. It is felt that a few good reasons, at least, have been advanced why the prevention of Rh isoimmunization in female patients is of vital importance. In conclusion, and without being overly dramatic, one may truthfully say that the transfusion of Rh+ blood into an Rh— girl or woman may constitute the death warrant of a child not only unborn but unconceived.*

Permission for the publication of these cases was very kindly granted by the following: Case No. 1, Dr. Edward L. King, Dr. Joseph W. Reddoch, and Dr. Thomas B. Sellers. Case No. 2, Dr. Edward L. King. Case No. 3, Dr. C. Gordon Johnson.

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*The grave prognosis given in case 3 has been justified by subsequent events. The patient exhibited increasingly strong antibodies and at seven months spontaneously delivered an Rh+ male infant who expired in thirty minutes. Postmortem examination revealed typical erythroblastosis fetalis, with hepatic and splenic enlargements, characteristic tissue changes and the presence of large numbers of immature erythrocytes in the peripheral circulation. The baby's cord blood contained Rh blocking antibody.

DIVERTICULOSIS OF THE COLON*

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Diverticulosis is a pathologic condition characterized by one or more diverticula in some portion of the intestinal tract. My paper is exclusively devoted to colon. These diverticula usually occur in multiple, more usually found segregated in some limited portion of the bowel and more frequently located in the sigmoid section of the left half of the large intestine. They are saccular pouches extending outwardly and lined with the mucous membrane of the bowel. For a long time they have been classified into two general types, the true and the false. In the former all the coats of the intestine are found, that is, the mucosa, muscularis, and the serosa; in the false type the muscularis is absent. Quite often the opening into these sacs is very small, which can easily induce retention of fecal material and subsequent inflammation. It has been found that in approximately 76 per cent of the cases the sigmoid flexure is the most common site of development and the most frequent site of diverticulitis. Most commonly the age of incidence is past 40, and the rate of incidence is 5 per cent. Especially prone are the older heavier persons who

*Presented at the Staff Meeting of Our Lady of the Lake Sanitarium, July 24, 1946.

lead a sedentary life. Frequently these saccular pouches border along the longitudinal bands. The possible complicatory developments are:

1. Diverticulitis.
2. Abscess formation.
3. Perforation with peritonitis.
4. Intestinal obstruction.
5. Internal or external fistula.
6. Carcinoma (descending order of incidence).

The symptomatology of diverticulosis without complications is characterized by constipation, chronic indigestion, flatulence, a recurrent dull tender ache in the lower half of the abdomen and a tenderness in the same area.

With inflammation there is pain in the involved side, fever, anorexia, tenderness and occasionally the passage of blood-stained mucus. A tumor mass may occasionally be found in the iliac fossa. These signs may be complemented with an abdominal rigidity of the involved half. However, not infrequently the abdomen may be soft and yielding to palpation. Not infrequently suggestive evidence of appendicitis may lead one to a hasty diagnosis of appendicitis.

When surgery becomes the elective approach a coloenterostomy is preferred. However, if the patient is very critically ill and surgical risk is at its maximum, a simple amputation of the diverticulum with plastic repair may be decided upon on laparotomy. If surgical risk encourages the surgeon a complete resection is done in behalf of therapeusis and prophylaxis. If surgery cannot be resorted to, the medical treatment for appendicitis may be rather efficacious.

I am especially interested in converging my interest in the particular complication of perforation with subsequent pelvic bacillus coli peritonitis. The following two cases will help to illustrate this phase of diverticulosis and convey the clinical picture for personal and professional estimate. These two cases are especially interesting because they ran a close parallel in mode of onset, progress and termination.

CASE NO. 1

Mrs. W. G., a white female, aged 82, was admitted to the hospital on May 7, 1946 and placed in bed for complete observation and treatment. This case, on admission, was categorized an acute medical emergency case.

She ate a hearty meal on May 6 at 10 a. m., and this was followed with pylorospasm and nausea with vomiting. Four hours later she developed a fever of 103 degrees. The following day, on May 7, prior to hospitalization, the patient went into shock at home, that is, she had a cardiovascular collapse. Her blood pressure dropped to 74, she was cold and clammy, in a semiconscious state and definitely in a very critical state. That evening I gave her two ampoules of coramine and then summoned an ambulance. She responded to emergency treatment and cardiovascular collapse was checked. The fever was rather high, but on the ninth day of May she definitely improved. Incidentally, streptomycin was begun at that time. My initial diagnosis on May 6 was Flexner gastroenteritis with cardiovascular collapse, but on May 7, I very quickly changed my diagnosis to sigmoid diverticulosis with perforation and subsequent bacillus coli pelvic peritonitis. During the course of this illness I became very much enthused over the fact that beginning with the ninth day of May, the patient began to improve and remained improved, but unfortunately in the morning of May 12, this patient very suddenly expired rather unexpectedly from possibly an embolus, a coronary thrombosis or an acidosis. On May 9, the patient had developed an uremia of N.P.N. 100, urea 50, and creatinine 2 but with the intravenous use of 20 per cent glucose, theophylline, salyrgan and digifoline the uremia improved to N.P.N. 63, urea 32, and creatinine 1.2 on May 11. Also the urinary output during these days improved from 8 ounces to 42 ounces. Blood count (5-8-46) white blood cells 12,850, SL 36, LM 2, polys 62. On May 9, hemoglobin 75, red blood cells 4,320,000, white blood cells 14,150, SL 28, LM 2, polys 69, E 1, no plasmodia found.

The sedimentation rate was: 15 min. 20, 30 min. 29, 60 min. 36.

Urinalysis on May 8 and 9 was negative.

Treatment: (emergency measures.) May 7:

1. Saline—10 per cent glucose, one quart.
2. Coramine—Two ampoules, intravenous infusion.
3. Digifoline—Two ampoules intravenously. One hypodermic every two hours for six doses.
4. Elevate foot of bed one foot.
5. Shock measures—heat.

(B. P. has risen from 76 to 140 systolic).

Routine Orders:

1. Digifoline ampoule, one hypodermic every four hours for eight doses.
2. Coramine ampoule hypodermic whenever necessary, if in shock and pulse weak.

3. Saline 10 per cent—Glucose one quart infusion daily.
4. Diet.
    1. Nothing ice cold.
    2. No soft drinks.
    3. No ice cream.
    4. No fruit juices.
    5. No grease or fried foods.
    6. No gravies.

    May have:
    1. Boiled milk served warm.
    2. Mashed potatoes—cream of wheat.
    3. Grits—oatmeal.
    4. Custards.
    5. Warm tea, coffee, cocoa, milk.
    6. Cool water.
5. Penicillin, 20,000 U. every three hours for sixteen doses.
6. Sulfadiazine, grs. 7½ tab., one every three hours, six doses daily.
7. Aspirin, grs. 5—whenever necessary for fever if high.
8. $NaHCO_3$ drahms ½, six times a day.
9. Catheterize p. r. n.
10. Sodium luminal, grs. 3, whenever necessary.

May 8, 1946:
1. Complete blood count repeated.
2. Sed rate.
3. N. P. N.
4. Catheterized specimen of urine to laboratory.
5. Continue digifoline, one ampoule every four hours.
6. Nothing by mouth.
7. No enemas.
8. Streptomycin has been ordered.

May 9, 1946:
1. Streptomycin every three hours.
2. Discontinue penicillin.

May 10, 1946:
1. Digifoline one ampoule, twice daily.
2. Salyrgan-theophylline intravenously.
3. Glucose 50 per cent intravenously.
4. Coramine—intravenously.
5. N. P. N. and creatinine.
6. Repeat blood count.

May 11, 1946:
1. Diet starting in a. m.:
    1. Grapefruit juice.
    2. Sweet lemonade.
    3. Coffee.
    4. Broth.
    5. Creamed potatoes.
2. Place under oxygen tent.
3. Upjohn's adrenal extract hypodermic 2 c.c. every four hours.
4. Amino acids parenteral (intravenously) Stearns.

CASE NO. 2

Mrs. E. F., a white female, age 60, was admitted to the hospital on August 30, 1944, per ambulance and placed in bed for complete observation and treatment. This case, on admission, was categorized an acute medical emergency case. In the early morning at 4 o'clock she was aroused with much pain in the lower abdomen with immediate nausea and emesis in about 20 minutes. She went to the kitchen for a cup of coffee, but had another spell of pain and vomited immediately after. She improved, however, sufficiently to return to bed and finish her night's sleep. During the early part of the day she did not feel quite well, so a doctor was summoned and at 8 p. m. she was admitted to the hospital. The patient was moderately tall, rather slender, somewhat emaciated, not apparently very ill on superficial observation, but revealing marked tenderness in the lower left quadrant of the abdomen along the left flank.

Patient stated that she had observed the passage of a black stool 24 hours prior to onset of present illness.

History: Present illness as revealed in preliminary resume.

Past History: Eight months ago she had an intestinal upset which responded to medical treatment, tenderness in lower abdomen with diarrhea, a spell of pleurisy in 1934, arthritis for a few years, appendectomy in 1935, no accidents, usual childhood diseases, no history of amebiasis or typhoid fever.

Family History: No history of cancer or tuberculosis in the family.

Physical Examination: General appearance: a white female definitely senile, impression age 65 or 70, well developed, but very poorly nourished, marginally emaciated, complexion not clear and somewhat sallow, dehydrated and run down. Head essentially negative, except for prominent tortuosity of the right temple artery, face wrinkled, skin soft and moist. E. E. N. T.: Essentially negative. Chest: Lung field clear. Abdomen: Right rectus incisional scar present and definite tenderness in left lumbar region radiating to the left iliac region (peristalsis normal, no palpable masses). Extremities: Negative. Vaginal: atrophic pelvic organs, tenderness in lower left quadrant and suggestion of a mass in that region. Rectal: Findings same as vaginal. Heart: (Chest) An occasional irregularity of rhythm, no murmurs, heart slightly small.

Progress: Patient did not improve, continued growing worse from day to day, and expired on September 18, 1944 at 6 a. m. Patient, during course of illness, developed a hypostatic pneumonitis and cardiac failure.

Laboratory Studies: August 30, 1944: white blood cells 19,850, 79 polys, L 20, M 1. Malarial smear, negative (thin smear-Wright stain). Urinalysis: Sp. 10.20; albumin heavy trace; sugar, free; crystals, none; casts, few hyaline; epith. moderate amount; white blood cells, occasional; red blood

cells, none. Blood Wassermann negative; Kolmer and Kahn, negative.

September 4, 1944: White blood cells 19,900, polys 73, L 25, M 2, red blood cells 8,000,000, hemoglobin 65.

Sed. rate: 15M-5M
30M-22M
60M-36M

Blood Chemistry 100 mg/cc.

N. P. N. 37.7 mg/cc; urea N 18 mg/cc; creatinine 1.3 mg/cc.

Urinalysis: Color, yellow; reaction, acid; sp. gr. 10.24; albumin faint trace; sugar free; indican, negative, acetone, negative; diacetic, negative; white blood cells occasional; red blood cells none; sulfadiazine crystals.

Differential diagnosis: Acute perforation posterior wall of the stomach with abscess of lesser peritoneal sac.

Perinephritic abscess left.

Carcinoma (G. I.).

Aneurysm (retroperitoneal).

Diverticulitis (sigmoid).

CONCLUSION

These two cases differ only in their duration. Case 2 survived for over three weeks and died rather suddenly, but never did get better. Case 1 survived six days and had actually improved, but unfortunately, she died from apparently an embolus, a thrombosis or an acidosis. In either case they did not develop an abdominal rigidity at any time during the course of the illness, but they both experienced a tenderness in the left iliac region where a palpable mass developed in the second day of their illness. The predominant features were: (1) Suddenness of onset; (2) shock; (3) fever; (4) pain and tenderness in lower abdomen to the left; (5) palpable mass; (6) no bowel movement; (7) nausea without vomiting; (8) general depression; (9) ashen-grey complexion; (10) vomiting following ingestion of a meal; (11) symptoms of gastroenteritis.

The one important thing about these cases which should be cited as a word of caution is that case 1 took a purgative. Case 2 had several enemas. These two things should definitely be placed on the prohibitive list. In conclusion I wish to say, for sake of emphasis, that any person, especially past 50, who is suddenly taken ill with symptoms of gastroenteritis complicated with toxicity, shock or semi-consciousness should be categorized into this particular group in the differential diagnosis.

AMNIOTOME

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The fetal membranes may be artificially ruptured to induce labor, to expedite the progress of labor, or to obtain the tamponade effect of the head in certain cases of placenta praevia. Obviously, rupture of the membranes should not be performed for the induction of labor unless there is a definite reason for terminating the pregnancy. If such an indication exists, then one must take into consideration the following: fetal size, presentation, position, station and condition; and the status of the cervix plus other maternal factors. The cervix should be soft, and its canal should permit the introduction of two fingers. Evidence of effacement is also a desirable indication of the "ripeness" of the situation.

Most obstetricians now agree that the advancing head is a better dilator than the hydrostatic bag which was so forcefully emphasized years ago. It is the general concensus that the distressful, long dry labors of the past were not the results of spontaneous early rupture of the membranes, but were due to faulty presentation, malposition, disproportion or other abnormalities.

On the Tulane Obstetrical Service at the New Orleans Charity Hospital, we have used various and sundry instruments to rupture fetal membranes before or after the onset of labor, but many of us have preferred to use one-half of a tenaculum.

Before the days of the box lock, it was easy enough to find a tenaculum which either had been discarded or was in such a condition that it was a candidate for the scrap pile. During recent years, however, such has not been the case. Therefore, it

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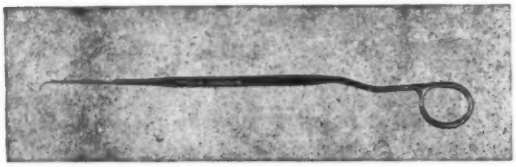
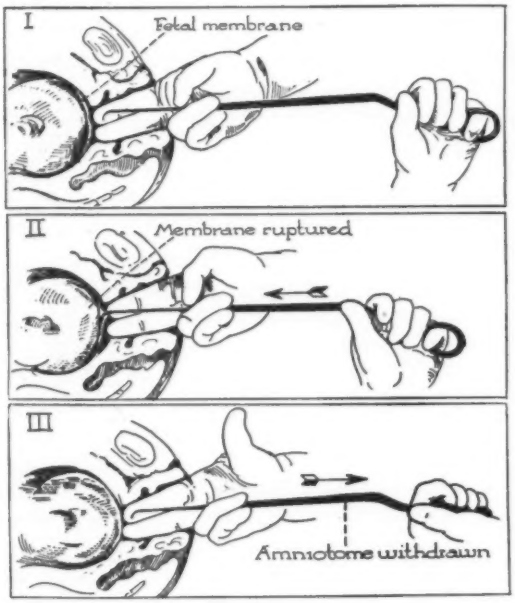
was advisable to design an amniotome* after the desirable features of our long-used and highly regarded "membrane hook." The result is shown in the figure,



the actual length of the stainless steel instrument being nine inches.



It will be noted that in maneuver I, the finger guards the tip of the amniotome. In maneuver II, the amniotome is brought into contact with the fetal membranes and manipulated in such a way that perforation of the membranes is effected. Maneuver III indicates how the amniotome is withdrawn so that the tip of the index finger again guards against possible trauma to any of the maternal structures. As shown, the fingers should be left in position until fluid ceases to flow at a rapid rate, rather than be withdrawn with the first gush of water. After use, the instrument should be cleansed with soap and water and then sterilized. For sterilization we are now employing 1:1000 Zephiran solution.

*The instrument may be obtained from the J. Sklar Manufacturing Company, 38-04 Woodside Avenue, Long Island City 4, New York.

THE TREATMENT OF GAMBIAN TRYPANOSOMIASIS*

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INTRODUCTION

In 1892 Laveran was able within the compass of a short article in the Archives de Médicine Expérimentale et d'Anatomie Pathologique to give a complete resume of all that was known concerning the trypanosomes. Only one pathogenic species was known and few people were interested in it because it produced only an obscure disease among livestock in India.

African sleeping sickness was described a hundred and forty-three years ago by Winterbottom in Sierra Leone but it was not until December 18, 1901 that Dutton and Ford recognized definitely for the first time that a trypanosome might occur in man and named this parasite *Trypanosoma gambiense*. Numerous bacteria, malnutrition, manioc poisoning and even a protozoan, *Filaria perstans*, had been blamed as the cause of sleeping sickness before this time. In 1903, after twelve more cases of human trypanosomiasis had been recorded, Castellani, examining the cerebrospinal fluid of natives with sleeping sickness in Uganda, discovered trypanosomes which were first called *Trypanosoma ugandense* (Castellani) and *Trypanosoma castellani* (Kruse). This observation was soon widely confirmed throughout Uganda and the Congo Free State.

It has since been shown that these two organisms are the same. A subspecies of *T. gambiense* which is morphologically indistinguishable from it but which causes a more severe human reaction and which is

*Awarded the Walter Reed Memorial Medal offered by the Louisiana State Medical Society for the best thesis on tropical or preventive medicine to a member of the senior class at Tulane Medical School.

resistant to arsenic therapy, was described in 1910 by Stephens and Fantham and named *T. rhodesiense*. They considered this organism a distinct species but different authors have suggested that it may be a variant of *T. brucei* or *T. gambiense*. *T. rhodesiense* is usually transmitted by *Glossina morsitans* while *G. palpalis* is the most common insect vector for *T. gambiense*. The conclusion of the International Commission on Human Trypanosomiasis was that the two trypanosomes were the same organism transmitted by different vectors.

EARLY MEANS OF THERAPY

It is interesting to read in Nabarro's translation of Laveran and Mesnil's treatise on trypanosomiasis (1907) of the early efforts at treatment of African sleeping sickness. The initial statement is: "Authors are agreed that sleeping sickness is always fatal. By careful nursing so that bedsores are prevented and the patients properly fed, one may prolong the life of patients, without, however, being able to prevent the fatal issue. Whether the prognosis is as grave in the first stage of the disease when the trypanosomes are not found in the cerebrospinal fluid, is at present undecided."

These authors recommended tonic treatment with iron, quinine and arsenic in the form of arsenious oxide of sodium arsenite. The discovery of the curative value of trypan red (Ehrlich and Shiga) upon caderas in mice had given great impetus to the study of the benzidine dyes as trypanocides. Atoxyl, described by Thomas in 1905, was showing great promise, especially in conjunction with trypan red or strychnine sulfate. The dose of atoxyl recommended varied with different authors from 0.6 to 1.5 gram.

In view of later discoveries it is interesting to note in more detail the work of Mesnil and Nicolle on the derivatives of benzidine. Numerous compounds were prepared and tested on various animals infected with *T. brucei*, *T. equinum*, *T. evansi*, *T. dimorpha*, and *T. gambiense*. Tolidine and dichlorobenzidine combined with 1, 8, aminonaphthol, 3, 6, disulphonic acid were the most effective in the first three infections. The two most effective compounds tested on *T. gambiense* were p-diamino-diphenylurea combined with 1, 8, aminonaphthol, 3, 6, disulphonic acid and p-amino phenylglycolether combined with the same acid. Although these dyes were not satisfactory trypanocides one notes how close these authors came to stumbling onto the diamidines which are receiving so much attention today.

Manson's manual of tropical diseases (fifth edition) published in 1914 was somewhat more optimistic than Laveran and Mesnil's work. Manson states: "Although something may be done to relieve symptoms and delay the fatal issue in the sleeping sickness stage of trypanosomiasis, it is only in the earlier stages of the infection and by the persistent and energetic use of arsenic or antimony, or both, that a cure can be effected, and that in a proportion of cases only."

The drugs which were in use at this time (1914) were atoxyl (soamine), arsenophenylglycin, arsacetin, and salvarsan. Manson recommended atoxyl given grains 3, intramuscularly every three days for two years in combination with tartar emetic. These and all other drugs tried, however, were found to be impotent in *T. rhodesiense* infections.

Atoxyl was the first really effective trypanocide discovered. Ouzilleau and Lefrou using atoxyl in doses of 1.0 to 1.25 gram combined with tartar emetic 0.05 to 0.1 gram reported a very favorable series. They gave a total of six injections over a twelve week period to 186 patients in the first or second class and had only 17 relapses after observation for over a year in 164 cases and over seven months in the remainder.

Contrary to the meaning of its name, atoxyl is extremely toxic. It combines the general toxic properties of all organic arsenicals with a special propensity for causing optic nerve injury. It is no longer employed in antiluetic therapy and is only rarely used in tryparsamide resistant cases in the treatment of trypanosomiasis.

Drug-fastness is easily produced with

atoxyl and Fulton and Yorke have demonstrated the permanence of the resistance by maintaining an atoxyl-fast strain for over 12 years with passage through 1528 mice.

TRYPARSAMIDE

Tryparsamide (sodium salt of N-phenylgycineamide-p-arsonic acid) was first prepared (1915) and described by Jacobs and Heidelberger in 1919. All of the early experimental work was done by Pearce and Brown in a manner which may be considered a classic in experimental therapeutics. The new drug was thoroughly and extensively tried out in *Trypanosoma brucei, T. gambiense, T. equinum, T. equiperdum,* and *T. evansi* infections in rabbits, rats, mice and guinea pigs, the therapeutic and lethal doses determined and the toxic symptoms and pathology were shown before the results were publicized. The efficacy of different methods of administration was tested and the intravenous route was found to be the best. Doses of over 0.3 gram per kilogram were found to be almost uniformly curative in all cases even when only one dose was given, and a single dose of only half this amount was highly effective. Special note was made that the drug seemed to have an excellent effect as a general tonic for animals in poor condition. Recovery from near lethal doses was rapid and complete and upon repeated administration the animals appeared to develop tolerance to the drug. Toxic reactions noted were tremors, clonic spasms, weakness, prostration, tics, anorexia, diarrhea, and weight loss. The pathology consisted of petechiae, effusions, cellular degeneration or necrosis of the kidneys, adrenals, cardiovascular system, gastrointestinal system, central nervous system and the blood and blood-forming organs.

In 1920 Dr. Pearce went to Leopoldville, Belgian Congo, where, assisted by Drs. Rodhain, Van den Branden and Van Hoof, she treated 77 cases of human infection with *T. gambiense.* She found that a single dose of 0.3 to 7.0 grams of tryparsamide produced sterilization of the blood in three and a half to 24 hours and with dosages of 0.5 to 5.0 grams the sterilization lasted three to six weeks. General physical condition was promptly improved, the subjective symptoms disappeared and temperature and pulse returned to normal in two to three days. Within a month the blood picture improved, the adenitis subsided and there was a gain in weight. Visual disturbances of a transitory nature were noted in nine of the 28 advanced cases. A number of relapses occurred during the brief period of observation but the results especially among those cases with central nervous system involvement were most heartening. A dose of 2 to 3 grams once weekly was recommended but the ideal total dose was still to be determined.

Chesterman in 1924 reported a series of 38 cases which had received 10 to 28 grams of tryparsamide and had been followed for one and a half to two years. Of 24 previously untreated cases nine were cured while of 10 who had previously received other arsenicals only three were well. The other four cases had been treated unsuccessfully by Marshall's serum method and three of these remained well after tryparsamide therapy. One case of blindness was reported.

In 1927 Kellersberger, Marugo, Lopes, Infante, and Van den Branden, reported 339 cases treated with tryparsamide of whom 220 were apparently cured. Many of these showed moderate or slight alteration of the spinal fluid. Trolli reviewed 1400 cases treated in the Belgian Congo prior to 1926 and stated that cure rates of 28 to 100 per cent had been obtained in the 896 cases with spinal fluid changes. Almost all of these recoveries were a true gain when compared with older forms of therapy which rarely cured an advanced case. Various dosages were recommended from 1.5 to 4 grams per dose once weekly to a total of 20 to 100 grams. Van den Branden reported a cure rate of over 17 per cent in late cases while Lauterberg stated that 60 per cent cures should be expected even in severest cases.

The most comprehensive survey of tryparsamide therapy to date is the monograph

of the Rochefeller Institute by Louise Pearce published in August 1930. She referred to 1848 cases and analyzed 1197 of these; 1101 were advanced in degree and 96 were early cases. She urged the administration of the drug in weekly doses of 0.05 to 0.06 gram per kilogram. Early cases should receive a total of 0.4 to 0.5 gram per kilogram. Advanced cases were best treated by graduated doses beginning with 0.02 to 0.05 gram per kilogram and gradually working up to a full dose of 3 to 4 grams. A first course of 25 to 30 grams was suggested for these advanced cases, to be repeated after several months and again if needed. The incidence of visual disturbances was 5 per cent, of permanent impairment of vision 1.8 per cent. The results which she reported following five to 31 months' observation were as follows:

No. cases	Apparent cures	Improved	Failures
96 (early)	89 (92.7%)	0	7 (7.3%)
1101 (advanced)	646 (58.7%)	272 (24.7%)	183 (16.6%)

Kellersberger, who has given 150,000 injections of tryparsamide for sleeping sickness, considers it the most useful drug in this disease. He advocates average weekly doses of 0.045 gram per kilogram and states that in order to be fully effective the drug must be pushed to the limit of safety. Low doses such as 2 grams routinely to adults or graduated doses are likely to produce arsenoresistant trypanosomes.

Hawking in 1940 ran a number of experiments comparing the plasma and cerebrospinal fluid levels of tryparsamide and various other trypanocidal agents (neocryl, undecaine diamidine, neoarsphenamine). He concluded that the ability of tryparsamide to penetrate the blood-spinal fluid barrier did not depend on the presence of trypanosomal lesions in the choroid plexus as other authors had suggested. The amount of tryparsamide in the spinal fluid (41 gamma of total arsenic at 17 hours), however, was insufficient to affect freshly isolated trypanosomes.

Fowler treated 42 cases of Gambian sleeping sickness by an intravenous drip giving 2 grams of tryparsamide daily for six to nine days. A rest was often necessary as the patients became exhausted with the high fever produced. In three patients visual acuity was almost lost; seven patients died from the treatment. The 35 survivors were clinically cured and four to seven months later 24 were reexamined and found to be well. In 33 of the 42 cases there was spinal fluid involvement.

Most authors have found that the maximum cure rate with the minimum number of accidents may be secured by using what is called the combined form of treatment. This consists of one or more 1 gram doses of Bayer 205 followed by a number of doses of tryparsamide. Harding and Lourie recommend one to three doses of Bayer 205 at weekly intervals followed by a rest of five to seven weeks and then by three to nine or more doses of tryparsamide. This method tends greatly to reduce toxic reactions since the kidney is allowed to recover before the arsenical is begun.

As has been mentioned before the chief toxic reaction to tryparsamide is the visual injury. Ideally all persons to be treated should have tests run to determine their visual fields and acuity. If any impairment is present great care should be exercised. Ordinarily close questioning during treatment will detect any visual disturbances before permanent harm is done. Most authors agree that these reactions almost always develop during the first eight to 12 injections or not at all. The incidence is reported as 5 to 10 per cent by various writers but only a small portion of these cases show permanent harm. In some cases sudden blindness may occur. The subjective complaints are usually blurring, haziness, spots or clouds before the eyes, shimmering, dazzling or blindness. Objectively narrowing of the visual fields or loss of visual acuity may be demonstrable.

Other untoward reactions include nitritoid reactions; mild jaundice, or very rarely liver atrophy; gastrointestinal disorders such as nausea, vomiting, diarrhea and abdominal cramps; desquamative dermatitis and urticaria. Cerebral symptoms may include dizziness, headaches, drowsiness, coma, convulsions, siezures, tremors, ting-

ling sensations, acute hallucinosis, foot drop, or emotional disturbances.

The possibility of the development of tryparsamide resistant trypanosomes was suspected as soon as the drug was discovered since it was well known that trypanosomes and spirochaetes readily became resistant to atoxyl and other arsenicals. This has been amply confirmed and De Brauwere has reported the development of a number of arsenic resistant foci of trypanosomiasis in the Belgian Congo. Yorke was able to maintain strains of *T. gambiense* for many years after they had been experimentally made arseno-resistant without appreciable loss of this characteristic. King suggests several modes of action of the arsonic acid group on the trypanosomes. Nonionized compounds may orient themselves at a water-lipoid interface while others may be absorbed on polar surfaces. The killing reaction probably involves the arsenoxide group and the mercaptan groups of the living cells.

BAYER 205

In 1920 Haendel and Joetten published an article dealing with a new Bayer preparation whose formula was kept secret on account of the position of German industry at that time. This drug, known as Bayer 205, showed a remarkable trypanocidal and prophylactic action in mice infected with *T. equiperdum*, *T. congolense*, and *T. brucei* and also in rabbits, rats, guinea pigs and dogs infected with various trypanosomes.

The composition of the drug has never been divulged by the manufacturers but substances apparently identical have been synthesized by other companies (Fourneau 309, Moranyl, Antrypol, etc.). It is a sulfonated naphthalene amidopolypeptide (see appendix for formula) with a relatively low toxicity. Large doses cause hemolysis and decreased coagulability of the blood and result in hemorrhages and nephritis. Degenerative lesions of the adrenal cortex were produced by Humphreys in animals with a dose one and a half to two times the maximum safe human dose (0.02 gram per kilogram).

Bayer 205 has little effect on trypanosomes *in vitro* but the serum of animals or humans which have received even one dose retains a trypanocidal action for weeks or months when injected into other infected animals. The sterilization of the blood is rapid in mice and slower in other animals. Various ideas have been suggested to explain the mode of action of this drug. Mayer and Zeiss after noticing that the trypanosomes were seen in dividing forms frequently after treating animals with Bayer 205 suggested that there was some interference or blockage of reproduction of the flagellates. Jasco and Hawking explained the action of the drug as an opsonizing effect but Dubois and Kohn were able to disprove this. These authors treated infected mice with moderate doses of Bayer 205 and 12 to 14 hours later injected blood from these animals into other uninfected mice whose reticuloendothelial systems had been blocked by electrocolloidal copper and splenectomy. These mice did not become infected so the authors concluded that the trypanosomes themselves had fixed a toxic amount of the dye.

The trypanocidal activity of the serum from healthy or cured animals or humans treated with Bayer 205 has received a good deal of attention. Boursnell and Wormall have shown that the drug is retained chiefly by the kidneys, spleen and plasma globulins apparently by a chemical combination. The serum proteins undergo a marked change on the addition of 2 per cent Bayer 205 solution. They become incoagulable by tannic acid, metallic salts or heating to 60° C. and fail to provoke an anaphylactic shock in sensitized animals due to a denaturation in which the sulfonic group is probably involved. A complex combination with serum calcium is probably concerned in the anticoagulant effect. Hawking was able to demonstrate a measurable amount of Bayer 205 in the plasma of individuals who had received eight to nine 1 gram doses eight to nine months previously. He also reported that there is a great individual variation in the plasma level produced in different persons by the same dosage. He found that the cerebrospinal fluid levels were too low

to measure even when the plasma level reached 15 mg. per cent. On the other hand, Kunert, in studying the blood and cerebrospinal fluid concluded that the blood level was two to four times as high as that in the spinal fluid and that the drug reached the spinal fluid by either means of administration.

The early reports on the efficacy of Bayer 205 were often enthusiastic. Kellersberger reported nearly 100 per cent cure in early cases treated with 5 to 10 grams. Kleine and Fischer after having poor results in 30 late cases treated 163 early with three 1 gram doses and found only two relapses among 90 of them six months later. Most of the workers reported excellent results in early cases but only fair or poor results after the nervous system had become involved. Strada and Lopes, however, treated 12 early cases and 31 late cases and obtained only one cure.

More recent reports have uniformly agreed that Bayer 205 should never be relied upon in late trypanosomiasis. Saunders followed 35 late cases for 13 years and at the end of that time 34 had died of sleeping sickness and the thirty-fifth had relapsed. He states that Bayer 205 will not cure central nervous system involvement but may produce remissions lasting for years. This fact is of value in the treatment of late cases which are arsenic resistant.

For the treatment of early trypanosomiasis Bayer 205 is recommended because of its low toxicity and high index of effectiveness. The average recommended dose for intravenous administration is 1 gram dissolved in 10 c. c. of distilled water. The total amount required to effect a cure is about 10 grams. Intramuscular injection is sometimes used. Intrathecal administration is to be condemned as it does not improve the effectiveness and produces pain, vomiting, headache, convulsions, and even death.

Bayer 205 is not, however, without toxic danger. A temporary nephritis evidenced by albuminuria is often produced and may terminate fatally. Other toxic reactions which have been noted are nausea, vomiting, fever over 40° C., palpebral edema, cutaneous hyperesthesia, photophobia, epistaxis, dermatitis, stomatitis, conjunctivitis, and urticaria. Idiosyncrasy to the drug with alarming collapse and one death was reported by Edge. He advocates a trial dose of 0.3 gram to avoid such misfortunes.

Hawking described three cases which relapsed five, nine, and 19 days after the last dose of Bayer 205. Chemical determination of the blood levels of the drug showed that there had been defective accumulation. The trypanosomes in two of these cases were proved to be non-resistant to Bayer 205.

Drug fastness to Bayer 205 has been demonstrated but different workers have gotten different results in determining the persistence of this resistance. Fulton and Yorke maintained a resistant strain of trypanosomes for over three and a half years without loss of fastness.

In the field of prophylaxis of sleeping sickness Bayer 205 has proved its greatest value. Van den Branden in 1927 gave two 1 gram injections to over 183 natives in a village in the Belgian Congo. All of these people had received semiannual examinations for the previous five years so the new infection rate was well established. Following the experiment the number of new infections dropped from 17 to three. Fain in 1943 administered 0.025 gram per kilogram to 4500 persons in an old focus of sleeping sickness and reduced the new case rate from 162 to 12. Other workers have obtained similar results. Van Hoof and his coworkers recommended a dose of 1.25 to 1.5 gram to adults repeated after three months. They strongly urge that persons so treated should be carefully examined before treatment and when giving the second dose to avoid masking an infection which is already established.

DIAMIDINE COMPOUNDS

The story of the discovery of the effectiveness of this important group of drugs is vividly portrayed by the address given by Professor Warrington Yorke before the Royal Society of Tropical Medicine and Hygiene. In 1911 Biot, Biot, Richard and Fleig showed that if glucose was added to

citrated blood containing trypanosomes the survival time of the organisms was prolonged. Later authors further investigated this phenomenon proving that enormous quantities of glucose were required in the metabolism of trypanosomes and that animals infected with these organisms exhibited varying degrees of hypoglycemia during the course of the infection.

Jansco and Jansco in 1935, having reached the conclusion that Bayer 205 acts by interfering with the carbohydrate metabolism of the trypanosomes, examined a number of guanidine derivatives, which were known to produce hypoglycemia, in the treatment of experimental trypanosomiasis. They found that a number of these compounds, notably synthalin, showed a therapeutic action against *T. brucei*. In the same year Schern and Artagaveytia-Allende concluded that the therapeutic action of synthalin was due to a toxic effect on the trypanosomes (*T. equinum*) as well as to the hypoglycemia produced. Proceeding further along this line in 1939 Lourie and Yorke proved that the therapeutic effect was not due to the hypoglycemia at all since the small doses employed had no significant effect on the blood sugar level and secondly that insulin had no trypanocidal effect. These authors, having developed a method for maintaining trypanosomes *in vitro*, went on to show that synthalin has a powerful, direct trypanocidal effect. Thus we see that after starting with a false hypothesis a really therapeutically active drug was discovered.

This discovery was of especial importance because synthalin did not resemble structurally any of the known trypanocidal substances.

Investigations were carried out by the National Institute for Medical Research and later by the drug firm, May and Baker of London, to determine what portions of the chemical structure of synthalin contained the trypanocidal activity. Numerous compounds were tested and several were eventually selected which showed very high trypanocidal activity. These were:

1. Undecaine-1, 11-diamidine
2. 4:4'diamidino diphenyl ether (phenamidine)
3. 4:4'diamidino stilbene (stilbamidine)
4. 4:4'diamidino diphenoxy propane (propamidine)
5. 4:4'diamidino diphenoxy pentane (pentamidine)

The last three compounds as well as a number of others which exhibited less trypanocidal activity have in common an inert carbon chain joined directly or through oxygen atoms to two diamidino groups. Relatively small changes in the polar groups such as changing them to a 3:4' or 3:3' position or replacement of one hydrogen by a methyl group completely destroy the trypanocidal activity.

Little progress has been made in determining the method of action of this group of compounds. One of the main difficulties is that no entirely satisfactory method has yet been devised for chemically estimating the absorption and excretion of the drugs. Hawking and others have made use of the blue fluorescence produced by 4:4'diamidino stilbene in ultraviolet light to show that it is absorbed by living trypanosomes, deposited in the liver, kidneys, and skin and excreted in the urine. The blood plasma level drops rapidly following injection into infected animals. A colorimetric method of analysis has also been described by Devine.

The metabolic effects of the 4:4'diamidino derivatives of diphenyl ether, stilbene, diphenoxy propane and of diphenoxy pentane have been carefully studied by Devine and by Wein and his coworkers. They reported that the diphenyl ether compound was slightly less toxic than the other three. The effects produced were a drop in blood pressure caused by peripheral vasodilatation, and a stimulation of smooth muscle. The first effect could be reduced by the administration of calcium or atropine but atropine did not counteract the smooth muscle stimulation. An ergotoxin-like effect was noted and the actions of adrenalin or the blood pressure, uterus and perfused vessels were reduced. Dosages on the therapeutic order of these drugs produced no

appreciable change in the blood picture or in the chemical constituents of the blood. Higher doses, some approaching the toxic level, produced hyperglycemia, raised blood urea and reduced serum calcium and potassium. Repeated high doses produced marked depletion of liver glycogen, fatty degeneration of the liver and cloudy swelling of the kidneys.

Following a report by Bowesman which seemed to indicate that old solutions of 4:4'diamidino stilbene showed increased toxicity Fulton and Yorke and other authors began to study this phenomenon. They found that the saturated diamidines were quite stable under all conditions and that solutions of the stilbene compound would withstand heat or storage in the dark but rapidly became more toxic when exposed to sunlight. Henry reports that this change occurs largely during the first six hours of exposure to a mercury arc lamp or to intense tropical sunlight. Several explanations have been offered. Barber, Slack and Wein believe that the toxicity is due to 4:4'diamidino phenyl benzyl carbinol produced by the addition to the unsaturated stilbene chain of water elements. Henry on the other hand is convinced that the amidine groups are changed into amido groups and possibly that polymerization occurs forming 1, 2, 3, 4-tetra (4'amidino-phenyl) cyclobutane. This point is yet to be settled and meanwhile the use of freshly prepared solutions of 4:4'diamidino stilbene will prevent the toxic reactions from occurring.

The clinical use of the diamidines has been limited almost entirely to three compounds—stilbamidine, pentamidine and propamidine.

McLetchie (Nigeria 1940) reported a small series of 14 cases treated with stilbamide. In eight mild cases he found that an average dose of 8.8 mg. per kilogram given intravenously over a nine day period was as effective as Bayer 205 but less so than the combined treatment. The short course of therapy is a great advantage over the older methods. Harding (Nigeria 1940) in a similar study of 13 cases agreed with McLetchie that only early cases responded favorably to this drug. He reported that in no cases with pathological spinal fluid was the drug effective. The dosage which he used varied in the cured cases from 3.2 to 8.0 mg. per kilogram. Bowesman (Gambia 1940) treated 36 cases with seven to ten doses of 1 mg. per kilogram. He agreed that in early cases the drug is effective and places the criterion that the cerebrospinal fluid protein must be below 0.05 per cent. He concludes that stilbamidine is the drug of choice in early trypanosomiasis because of its low toxicity, relatively high effectiveness and the short period required for its administration. Lourie (Sierra Leone 1942) reported 153 cases treated with stilbamidine. Of the 136 which were not far advanced 128 were traced for over a year and 51 of these were well. The dosage was one to eight doses of 50 mg. The author concluded that this drug is less effective than either propamidine, pentamidine, or tryparsamide even in early cases.

Pentamidine has been used on a fairly large number of patients. Saunders reported a high cure rate (11 out of 12) in cases with less than 30 cells per cu. mm. in the spinal fluid. About half of 35 cases with a higher cell count were improved but relapses were common. He recommended a dosage of 2 mg. per kilogram of body weight. Harding reported excellent results in 192 cases using eight to 12 daily doses of 50 to 100 mg. He considers this the drug of choice for cases with a spinal fluid cell count below 10 to 15 per cu. mm. Lawson and Gilbert after reporting series of 53 and 14 cases respectively also urge the use of this drug in early cases because of its low toxicity and effectiveness. The maximum dosage which may be given without toxic manifestations is 2 mg. per kilogram twice weekly since the drug tends to accumulate.

Van Hoof, Henrard, and Peel found that a single dose of 2 to 3 mg. of pentamidine per kilogram produced a prophylaxis lasting 10 to 12 months in two volunteers. Fulton using mice was able to demonstrate a prophylactic effect lasting up to four weeks.

The toxic reactions to the diamidine

drugs may be divided in two groups; those which occur immediately and those which are delayed. The former are quite common, the latter relatively rare. Immediate effects are usually those associated with a sudden fall in blood pressure—rapid, thin or imperceptible pulse, sweating, dizziness, faintness, unconsciousness, epileptiform twitchings and rarely incontinence are seen. Other effects may include salivation, nausea, vomiting, a puffy suffusion of the face and eyelids, severe pruritis, headache, rigor, palpitations, a sense of pressure in the head, albuminuria, and leukopenia. Lourie states that these effects were so severe following the use of stilbamidine that sooner or later an immediate fatal collapse is to be expected. Harding reported that he has used the isethionate instead of the hydrochloride of pentamidine in 150 mg. doses intramuscularly in 200 cases and he has found that the unpleasant side effects of the hydrochloride are eliminated.

Delayed toxic results have been reported by several authors. Wein, Frieman and Scotcher report cloudy swelling of the kidneys and fatty degeneration of the liver following the administration of repeated high doses to animals. Daubney and Hudson produced severe fatal fatty degeneration of the liver associated with edema of the gastric mucosa in a healthy calf which received three injections of 5 mg. per kilogram of stilbamidine at seven day intervals. The calf was killed "in extremis" on the twenty-eight day. Napier and Guptal[140] reported that three to four months after the administration of stilbamidine for Kala-azar six patients developed anesthesia to light touch over the trigeminal area and one over the distribution of the third cervical nerve. This lesion was non-progressive with a tendency to spontaneous cure after several months. McComas and Martin have reported a fatal case following the administration of three injections of 100 mg. each of freshly prepared pentamidine. These were given over a period of four days. After the first two injections the patient, a 28 year old Gold Coast soldier, complained of pain in the left temple. Ten minutes after the third injection he passed into a status epilepticus. The fits were controlled with intravenous pentothal but except for two brief occasions he remained unconscious until his death 14 days later. Autopsy revealed the typical findings of trypanosomiasis (lymphadenopathy, perivascular cuffing, flattening of the brain cortex and thickening of the meninges), early fatty degeneration of the liver and bronchopneumonia. Since the patient's blood had been repeatedly negative for trypanosomes upon animal inoculation after therapy was begun the authors concluded that the death was probably due to a Herxheimer reaction.

One marked advantage of the diamidines which remains to be studied more carefully is the apparent reluctance of trypanosomes to become resistant to them. Fulton, Yorke and Lourie were able to prepare resistant strains with considerable difficulty using synthalin and undecaine diamidine and these strains lost their resistance within three years. Similar resistant strains prepared using tryparsamide and Bayer 205 have retained this characteristic for many years. These authors also demonstrated that resistance to the diamidines was unrelated to resistance to other trypanocidal drugs.

MISCELLANEOUS MEANS OF THERAPY

Neocryl: This drug (sodium succinanilomethyl-amide-p-arsonate) has been studied by Acres, Murgatroyd and MacQueen. Murgatroyd treated 122 cases, 44 of whom had normal spinal fluids. He employed a routine course of 10 doses of 0.045 gm. per kilogram of body weight given at weekly intervals. Of thirty early persons who completed the course all were clinically improved but one relapsed 16 weeks later. Forty-six late cases completed treatment and 35 of these were clinically improved. However in four cases the trypanosomes never disappeared from the spinal fluid. Visual disturbances occurred in several cases. Murgatroyd believes that the results with this drug are similar to those with tryparsamide.

MacQueen noted rapid clinical improve-

ment in 60 cases. The blood and lymph were cleared of trypanosomes at the second examination. In two cases there were visual disturbances, one of which became entirely blind and expired within a month of cerebral trypanosomiasis.

Acres treated nine early cases with three relapses and twelve late cases with nine relapses. The period of observation lasted two years. The author states that the relapse rate in the advanced cases compared very unfavorably with that obtained using tryparsamide in the same area. Four of the relapses were retreated with no improvement and then two of them were resistant to tryparsamide.

Arsenobenzene: Arsenobenzol has been found to sterilize rapidly the peripheral blood of mice infected with *T. brucei*. Whether it is rapidly changed *in vivo* into an arsenoxide is unknown. Radna tried injecting 1 mg. of this compound into the spinal canal of seven persons suffering from sleeping sickness. This apparently increases the permeability of the blood-cerebrospinal fluid barrier thus greatly improving the effectiveness of such trypanocidal agents as tristibene and Bayer 205.

Azoarsenobenzol: Friedham treated 41 patients with eight to twelve doses of 0.5 gm. of azoarsenobenzol 4197 given every two to four days. Peripheral sterilization was complete in 38 cases after the first injection and in the remaining three after the second injection. There was rapid clinical and spinal fluid improvement and no toxic results were noted.[147] A longer period of observation will be necessary before the drug can be properly evaluated.

Triazine Arsenic Acid: Friedham and Muraz have reported very favorably on the use of the disodium salt of 2:4-diamino-6 (arsonoanilino) triazine. They used six to ten injections of 0.03 to 0.5 gm. per kilogram given every three days. Blood sterilization was rapid following one injection. Friedham treated 89 cases and obtained a rapid reduction in cerebrospinal fluid cells and a slowed drop in the albumen; 29 of these cases examined two and a half to nine months later showed no relapses. He also states that when compared with tryparsamide in mice triazine arsenic acid is eight times more active and less toxic.

Gamma-(p-arsenosopheny)-butyric acid: Eagle reports that this drug is stable in solution and in mice and rabbits has a slightly greater chemotherapeutic index than tryparsamide. In 2 per cent solution it is practically non-toxic. He has treated 200 patients in the Gold Coast, Nigeria, Belgian Congo and West Africa with six to twenty-four injections one to seven times weekly of 0.25 to 0.5 mg. per kilogram intravenously and intramuscularly. One important feature is that this compound is effective against "arseno-resistant" trypanosomes *in vitro*, in animals, and in man. Peripheral sterilization requires less than 60 minutes. The results have been gratifying in early cases but not too good in late cases where it may cause encephalitis.

Etharsanol, Proparsanol: Etharsanol (monosodium salt of 2-p-arsono-arsilino-ethanol) and proparsanol (monosodium salt of 3-p-arsono-anilino-propanol) each containing 20 per cent arsenic have been recommended for the treatment of trypanosomiasis. Stratman-Thomas, Lovenhart, and Van den Branden found etharsanol comparable in effect to tryparsamide but both of these drugs are more likely to produce ocular disturbances than is tryparsamide.

Phenanthridines: A number of compounds of the phenanthridine series have been found to be effective against *T. congolense*. Notable among these is 7-amino-9-(p-amino-phenyl)-10-methyl phenanthridinium chloride. Their effect against *T. gambiense* seems to be much less than that against *T. congolense*.

Antimonials: Many antimony compounds have been tried in trypanosomiasis. In *T. gambiense* infections these have all failed to prove as effective as the arsenicals. Among those which have been used are: stilbamine, stilbenyl, neostibosan, neostam, tartar emetic, antimony sodium thioglycollate, anthiomaline, fuadin and antimosan.

Bismuth Compounds: Kolmer, Kast and Rule have shown that the relatively high

concentration of 1:2400 is required *in vitro* for immobilization of *T. equiperdum* by potassium bismuth tartrate, sodium bismuth tartrate or bismosol. The immobilization correlates fairly well with trypanocidal action as determined by mouse injection tests.

Atabrine: Atabrine (erion, quinacrin, mepacrine, chinacrin) is absorbed by trypanosomes *in vitro* and Hawking has shown that it is slightly trypanocidal *in vitro*, although Fischly and Singer state that there is no trypanocidal activity *in vitro*. De Borchgrave and others have shown that this drug and argoflavine both have a trypanocidal action *in vitro* in dilutions as high as 1:30,000 and 1:15,000. The presence of the orthoquinoid radical prompted Lourie and Collier to investigate whether there is any risk of producing resistance to the arsenic compounds and non-metallic dyes containing similar groups. They concluded that there was no such danger.

Sulfonamides: P-aminophenyl-sulfonamide, sulfanilamide, and the other sulfonamides exert no deleterious effect on *T. brucei* or *T. equiperdum*.

Penicillin: Attempts at the treatment of Rhodesian trypanosomiasis and experiments using *T. cruzi* and *T. congolense* have shown that penicillin is ineffective against trypanosomes.

X-rays: The direct lethal dose of x-rays is not the same for all types of trypanosomes. The M. L. D. varies from 100,000 r. to 600,000 r. Only 2 per cent of this amount is required to prevent normal division.

Anticoman, Surfen, Congasin-Bayer: These three compounds were reported by Brauss in 1944 following experiments begun in 1939 and interrupted by the war.

Anticoman, a guanidine derivative, failed to cure *T. brucei* infection in mice although it cleared the peripheral blood in 24 hours.

Surfen appeared to act in a manner similar to Bayer 205 although not so effectively. It also has a less prolonged effect. The author concluded that it would probably be a useful trypanocide. It was also effective against *T. equiperdum* but ineffective against *T. congolense*.

Ethylenediamines: Funke, Bovet and Montezin prepared and tested 39 compounds of ethylenediamine on mice infected with *T. brucei*. Eight of these showed some effect; the best was (p-isopropyl-benzylamino)-1-amino-2-ethane. Activity seemed to depend on the presence of the diamine group and on a second substituted group in the benzene ring.

SUMMARY

1. A brief introduction and historical sketch of the discovery of the cause of African sleeping sickness is given. Early methods of therapy, notably with atoxyl, are mentioned.

2. The early reports on the efficacy of tryparsamide are given and the best modern methods of treatment by the use of the drug are outlined. The cure rates in early and late stages and the toxic manifestations are mentioned. Combined treatment as advocated by numerous authors consists of one to four doses of 1 gm. of Bayer 205 followed after several weeks by three or more doses of tryparsamide at weekly intervals.

3. The method of action, prophylactic effect, toxic reactions and efficacy of Bayer 205 are discussed. This drug when used alone is recommended only in early cases.

4. The development, metabolic and toxic effects and clinical results of the diamidines are described. Eight to twevle doses of 50 to 100 mg. of pentamidine produces excellent results in early cases. A prolonged prophylactic action has been demonstrated.

5. A number of newer drugs are mentioned. Among those which show promise of value are neocryl, azoarsenobenzol, triazine arsenic acid, gamma-(p-arsenosophenyl)-butyric acid, etharsanol and surfen.

It has been necessary to delete the references to this article because of their large number, namely 171. The reference list may be reviewed in the office of the editor by anyone who is interested in going over this complete bibliography.

BIOTIN

BRUCE W. ALSPACH, M. D.
NEW ORLEANS

The term vitamin was first used by Funk in 1911 to describe those indispensable food substances which man cannot synthesize in adequate amounts and which, therefore, must be obtained from food. The number of these substances is large and constantly increasing so that the general practitioner and medical student has long since fallen behind in the evaluation and utilization of those vitamins which have been isolated and described recently. A paper such as this therefore serves a definite purpose in correlating the available information and appraising the value of one of the more recent vitamins—biotin.

HISTORICAL

The history of biotin goes back to 1901 when Wildiers, working in Ides' laboratory in Louvaine, Belgium, described a compound called "bios" which was essential for the growth of yeast. This compound has since proved to be multiple in nature and from it, thiamine, pantothenic acid, pyridoxine and several other substances have been fractionated.[15]

One of these fractions, tentatively labelled Bios IIb was investigated further by Kögl. He succeeded in isolating from egg yolk a crystalline methyl ester of a compound which possessed the greater part of the yeast stimulating factor of Bios IIb and which he called biotin. Kögl[45] worked extensively with the substance, describing some of its chemical and physical characteristics and gave it the empirical formula of $C_{11} H_{18} O_3 N_2 S$.

Previous to these experiments by Kögl other investigators, particularly Allison, Hoover and Burk, had described concentrates which were growth and respiration promoting on certain strains of Rhizobium, a legume nodule organism.[1] These concentrates were derived from either commercial sucrose, hydrolyzed yeast or cultures of azobacter. Since the active substance was a co-enzyme of respiration it was called "co-enzyme R." Six years later, in 1939, West and Wilson postulated that co-enzyme R and biotin were identical.[95] This fact was proved that same year by workers in Sweden.[63]

In another field of biologic investigation, apparently unrelated to the two already mentioned, Boas in 1927 reported a syndrome which occurred in rats when dried egg white was added to their diet.[3] On this regime the rats lost their hair and a dermatitis, skin hemorrhages and loss of weight occurred, followed by a marked spasticity and then death. Boas describes a "protective factor X" present in raw potatoes, yeast and liver which would both cure and prevent the syndrome. The etiology of this "egg white injury syndrome" and the nature of the protective substance remained unknown for some time, although much information was obtained by numerous groups working on the problem. Findlay and Stern[21] suggested that it was a lack of a vitamin-like substance which caused the syndrome, and Sollman and Goodman later showed that drying the egg white had no effect on the occurrence of the egg white injury since it could be produced by using the fresh material as well.[85]

The protective factor was intensively studied by Parsons and her associates[68] who reported that the toxic factor in egg white was apparently protein in nature. They elaborated on the symptomatology in the rat,[49] and other animals,[50] and described further the protective factor.[69, 70] György and co-workers reported on the chemical and physical properties of the protective factor which he called "vitamin H", from the German "haut" meaning skin, referring to the dermatitis produced in the deficiency state.

Early in 1940, György joined the Cornell group of du Vigneaud and Melville. A short time later, the possible identity of vitamin H with biotin and co-enzyme R was suggested and in that same year the fact was established by vitamin H assays of a sample of biotin supplied by Kögl.[33] This was confirmed by the demonstration of the vitamin H activity of biotin from liver concentrates which contained a high index of vitamin H.[29] Thus three ostensibly different fields

of investigation each concerned with an extremely biologically active compound with well-defined actions were brought together by the demonstration, through persistent and often brilliant research, of a common identity and common actions.

CHEMISTRY

In spite of the progress made in identifying and analyzing biotin, only the empirical formula suggested by Kögl in 1938 was available. This formula was subsequently modified in 1942 by du Vigneaud[16] and associates to $C_{10}H_{16}N_2S$.

This compound, which is a monocarboxylic acid of high molecular weight, appears in crystalline form in long, thin, plate-like needles. It has a melting point of 230°—232° and is bicyclic in structure, one ring representing a five membered urea structure and a ring sulphur in a thio ether linkage possessing a six carbon straight moiety. Biotin is optically active and is easily destroyed by hydrogen peroxide, by peroxide containing ether and by nitrous acid.[28] Rancidified fats will also inactivate pure biotin, apparently by a partial oxidation. The end product is the same as that obtained when hydrogen peroxide is allowed to act on biotin.[73]

Pure biotin is one of the most active substances known, its effect on certain yeast strains being noticeable in a concentration of one in four hundred billion. This may be contrasted with the effect of ephinephrine on the frog's pupil in a one in twenty million dilution.[40]

As would be expected from the amount of work done on biotin, a large number of similar and related substances have been produced. The monomethyl ester of biotin was prepared from liver by du Vigneaud and his associates in 1941.[17] This is similar to the crystalline derivative of Kögl[46] prepared from egg white. The difficulty of obtaining biotin for investigation is exemplified by the fact that only one milligram was produced from a quarter of a ton of dried egg yolks.

In addition to the methyl ester, desthiobiotin has been isolated, a compound similar to biotin with the sulfur atom removed and replaced by two hydrogen atoms.[54] It has approximately the same activity as biotin on certain micro-organisms, but does not stimulate the growth of *L. casei* unless biotin is present. A large quantity of desthiobiotin, however, will inhibit the action of biotin.[51, 55] This would suggest that certain organisms have the ability to convert desthiobiotin to biotin and utilize this latter substance. Leonian and Lilly have shown that where desthiobiotin is capable of replacing biotin, the micro-organisms utilize only 40 per cent of the available substance present.

Less important related substances, some of which are isomers of biotin, are dl-biotin which is half as active as biotin, l-biotin which is one-fourteenth as active and allobiotin which is inactive. O-heterobiotin is an analogue of biotin in which the S in the thiophene ring is substituted by an O. It is about one-fourth as active as biotin.[14] Biotin sulfone has about 0.1 per cent of the growth promoting properties of biotin and must be given in tremendous quantities to cure egg white injury.[12] Diaminocarboxylic acid is derived from biotin by heating it with an alkali under proper conditions, thus splitting the urea ring. It has from 3.6-10 per cent of the activity of biotin.[19]

After the identification of the specific molecular structure of biotin it was only a matter of time before this substance could be synthesized. Success in this was first reported by Harris, Wolf, Mozingo and Folkes[34] in 1943. Subsequently investigation has proved this substance to be identical in every respect with the natural occurring material.[86, 66, 19] The fact that the synthetic substance has in its make-up three different asymmetrical carbon atoms makes possible the existence of several stereochemical isomers related to biotin, all with varying activity, of which a few may be listed. Synthetic dl-desthiobiotin is 50-60 per cent as active as the natural compounds but has only 0.1-0.01 per cent of the activity of biotin in rats.[80, 101] The synthetic equivalent of diaminocarboxylic acid, dl-diamino acid sulfate, is 4-7 per cent as active as biotin.[86]

METHODS OF ASSAY

The earliest methods of assay were both cumbersome and time consuming, for although biotin occurs widely in nature it is in exceedingly small concentrations. Animal assays, using the rat, were utilized by György[27] for his determinations of vitamin H. The chick has been suggested for the same purpose,[29] but these methods are no longer used and those based on the acceleration of growth of micro-organisms by biotin are in vogue at present. There are no chemical methods available for this determination.

Kögl measured the growth of standardized yeast strains over a five hour period as an assay method. In 1940, Snell, Eakin and Williams[84] described the most popular procedure in use today. They utilize the measured growth of a small seeding of Saccharomyces cerevisiae after a twenty hour incubation period in a synthetic media devoid of biotin. The incubation period has since been reduced to sixteen hours and Hertz[37] has widened its range of usefullness. The use of micro-organisms for the assay of biotin has been suggested and includes *Lactobacillus arabinosis*,[103] *Rhizobium trifolii*,[96] *Clostridia butylicum*[46] and *Lactobacillus casei*.[83] This last named organism has been used by Peterson and associates as a basis of a micro-biological test which they report to be accurate to within ten per cent. It has been shown since to have a wide application for assays of vitamins in the B complex group.[47]

In these micro-biological tests biotin should be present in the free form and not as the methyl ester which slows the growth and fermentation of the yeast.[87] A pH of 6.8 has been found most favorable for the estimation.[29] Extraneous growth stimulants which might cause an error in the determination are thought to be lipoid in nature and may be removed by simple filtration of the aqueous extracts.[98] Trager has shown that these methods are not applicable to the estimation of biotin in the blood.[93]

DISTRIBUTION

As has been previously stated biotin occurs extensively in nature, always however, in low concentrations. This is shown by the fact that liver, the richest source of biotin, contains less than 0.0001 per cent of the vitamin. The only other foodstuff comparable to liver in its content of biotin is the kidney. Beef, cereals, yeast, peptone, egg yolk, malt and alfalfa, all have comparatively large amounts of biotin. Chicken meat, vegetables and fruits, however, offer only fair quantities. Cooking appears to affect the biotin content to a minimal degree. Schweigert and co-workers found that 77 per cent of the biotin content of meat was retained after cooking. From 1-5 per cent of the biotin was recoverable from the drippings, making a total retention of 78-82 per cent of the original biotin content of the meat.[81]

Separate sections will be devoted to the occurrence of biotin in the bowel and tumor tissue, urease, muscle phosphorylase or any of the crystalline enzymes-catalase, renin, urease, muscle phosphorylase or concanavillin A.[56]

BIOLOGICAL SIGNIFICANCE IN YEASTS, VACCINIA AND BACTERIA

Biotin is a respiratory catalyst and as such is an essential nutrilite which most strains can synthesize to some degree.[44] The extent of this ability, however, is dependent on the synthesizing abilities of the cells used and the composition of the medium. It is reasonable to believe that, since all the synthetic processes of a cell are closely related, the presence or absence of one essential metabolite would affect the nutritional requisites of the others. Williams, Eakins and Snell have shown that biotin synthesis was facilitated by the presence of other essential metabolites such as, inositol, thiamine, pyridoxine and pantothenic acid. While synthesis did occur before the addition of any of these metabolites it was at a very slow rate.[99] To repeat, therefore, it cannot be said that the nutritional need by yeasts for any one substance of this group is absolute, but rather dependent on the presence of other substances. The ability of certain strains of yeast to convert desthiobiotin into biotin has already been stated.

A great deal of work remains to be done in order to clarify the importance of biotin

to vacinnia. Hoagland and associates[39] have shown that elementary bodies of vacinnia possess a concentration of biotin approaching that of egg yolk, liver and molasses. They foud a marked concentration of biotin parallel with an increase in viral activity. We know therefore, that biotin is intimately associated with the enzyme systems of vacinnia, although how essential it is has not yet been determined.

Bacteria may be compared to the yeasts in that biotin is an essential substance required by them. Their need for an exogenous supply of this vitamin is governed almost entirely by the relative ease with which they are able to synthesize it. In a strict sense, it would be incorrect to separate the bacteria for which biotin is essential, as determined by a complete absence of growth in a biotin-free medium, and those bacteria for which biotin merely acts as a growth stimulant. This latter phenomenon is due to the slow rate of synthesis by the bacteria, allowing a stimulation to be seen on the addition of biotin.

Those that cannot synthesize biotin and require an exogenous supply are certain strains of Rhizobium, Clostridium, Lactobacillus, Streptococcus and Brucella. Certain strains of Proteus and *Staphylococcus aureus* are capable of synthesizing biotin slowly and therefore they show only a slight stimulation on the addition of biotin. *Mycob. tuberculosis, B. subtelis, E. typhosa, Esch. coli, B. anthracis* and strains of Pseudomonas all synthesize biotin easily and show no change when biotin is added to media containing them.[44] In spite of these widely varying powers of synthesis, Thompson[91] has shown that the bacteria cell content of biotin remains constant. We may assume then, that the production of biotin by bacteria, which Thompson has shown to parallel the rate of bacteria growth, is a result of overproduction and not cell autolysis.

A large percentage of the bacteria capable of synthesizing biotin are normal inhabitants of the intestine of both man and animals. Wegner and associates[94] have shown that biotin is synthesized in large amounts in the rumen of the calf. The biotin content of the rumen is about five times greater than the original a few hours after feeding. The rumen of the cow and the cecum of the rat are the main centers of biotin synthesis in these animals.[53, 58] In man this synthesis takes place in the terminal ileum and large gut.

The efficiency of this synthesis is very high since rats on a biotin-free diet thrive well. Those on a biotin-low diet are able to excrete the vitamin in amounts that greatly exceed the intake.[60] Similar results in man have been described by Opell[64] who reported that three to six times the biotin content of the diet was excreted in the urine and stools of his subjects.[64] The work of Najjar and Holt[59] suggests that the bacterial synthesis of biotin in man is adequate for his needs.

The diet will obviously affect the quantity of synthesis taking place in the bowel both by changing the media upon which the bacteria act and by causing marked differernces in the intestinal flora itself, with corresponding changes in the products of those bacteria. Dextrin and dextrin containing carbohydrates appear to promote intestinal synthesis, as does roughage which increases the amount of unabsorbed food substances that provide an ideal medium.[58, 26] The interrelationship between the various vitamins is demonstrated in the rat by the decrease in biotin synthesis when a pantothenic acid or riboflavin-low ration is used.[61]

AVIDIN

Boas used egg white to produce the first biotin deficiency syndrome in rats. It has since been shown that this is due to the formation, in the gastrointestinal tract, of a non-absorbable complex between biotin and a constituent of the egg white. This substance which was named 'avidin' because of its avidity for biotin has been isolated in crystalline form. It is a basic protein of high molecular weight which combines with the biotin in a ratio of one molecule of biotin for one molecule of avidin.[102] The avidin-biotin complex (AB) cannot be dissociated in the digestive tract since it is un-

affected by the proteolytic enzymes pepsin, trypsin, pancreatin and papain.[30] It is also unaffected by changes of temperature and acidity and is therefore excreted in the stool.[31]

The only way that biotin may be released from this combination is by steam sterilization or by irradiation in the presence of riboflavin.[32, 48] In vivo this may also be accomplished by parenteral administration of the complex, apparently thus making biotin available to the body since egg white injury may be cured in this manner.[32] Proteins associated with eggs are the only ones which exhibit this pronounced biotin combining tendency.[38] It is interesting to note that avidin will inhibit the growth of those bacteria for which biotin is essental and affect only minimally those that are able to synthesize satisfactory amounts of the vitamin.[48]

The nature of the biotin-avidin combination is still unknown. It has been suggested, however, that both the cyclic urea and the aliphatic side chain are essential for the formation of this complex. When they are hydrolyzed, as in diaminocarboxylic acid, a combination between this acid and avidin will not take place.[13]

The question of the existence of an avidin-uncombinable biotin is still open to speculation. There is some evidence that large amounts of rat or human urine contain quantities of such material but it has not yet been proved that it has biotin activity or that, since it is found only in the urine it is not a partial break-down product of biotin.[8]

IN RATS

Induced biotin deficiency in rats is essentially the egg white injury syndrome which has been produced and described many times.[20, 62, 71] Characteristically, within the first two or three weeks on a synthetic diet, which ordinarily allows good growth, to which ten per cent egg white has been added, there occurs a loss of the long guard hairs of the body, leaving a soft mole-like coat. This is usually accompanied by an exfoliative, pruritic dermatitis, commencing on the abdomen and progressing to a generalized alopecia. A change in the color of the fur may also take place. Frequently, red scaly patches form at the corners of the mouth together with a reddening and swelling of the eyelids, giving a "spectacle eye" appearance. The animal's weight begins to fall and symptoms referable to the nervous system appear in the second or third week of the deficiency. The back becomes arched and the limbs spastic giving an abnormal "kangaroo-like" posture. Terminally there is a rapid loss of weight and cyanosis. Histopathologically in the acute deficiency state there is early atrophy of the thymus and testes as a manifestation of an ageing process. The skin shows marked drying and scaling with almost complete sloughing of the stratum corneum. Liver stores of biotin are greatly reduced and the stores of body fat are almost completely depleted.[3] Skeletal muscles are pale and striated and atrophied terminally.[82] The creatine content of the muscles has been shown by Pizzolato and Beard[76] to decrease on an average of 20 per cent in 136 days of a biotin deficient diet.

Despite the extreme spasticity observed clinically no degeneration of the spinal cord or peripheral nerves exists, nor is there at any time during the deficiency an impairment of the motor nerve to elicit tension in its muscles. It may be noted at this time that all these changes are reversible and the administration of crystalline biotin quickly brings about a complete remission of symptoms.

Daft, Ashburn and Sebrell[10] first noted that the symptoms of biotin deficiency could also be produced in rats by the administration of sulfaguanidine or sulfasuxidine in purified diets. This deficiency is usually complicated by deficiencies in other vitamins, particularly in folic acid, which are synthesized in the intestinal tract. Frequently, too, leukopenia and kidney lesions develop as specific effects of the sulfonamides and these may be relieved, not by biotin but with other measures, including the administration of whole liver. Remission of this deficiency or a protection from it could be obtained by treatment with biotin

and sometimes folic acid.[57] These findings have been confirmed by other workers.[52]

The mechanism of the production of this deficiency is predictable when the role of intestinal synthesis of the vitamin is recalled. The sulfonamides used are non-absorbable and as such act chiefly on the bacterial flora in the intestines, reducing their number and thereby reducing the amount of vitamins synthesized. This leads to the production of a deficiency. The concept has received almost unquestionable support and has a large amount of experimental evidence to corroborate it.[11] There is no proof, however, that the inhibition of the bacterial synthesis of biotin and not some other factor of the sulfonamides caused the deficiencies. It may also be noted that there are other observations which are difficult to reconcile with this theory.[10]

The mode of action of biotin in animal tissues appears to be as a component of an enzyme system concerned with the metabolism of pyruvate. On a biotin deficient diet rats show decreased rates of oxidation of pyruvate by the liver.[75] This is similar to what occurs on a pantothenic acid deficient diet and therefore suggests a close relationship between these two vitamins. Wright and Welch[104] have shown that pantothenic acid cannot be utilized in the rat except in the presence of biotin.

There is also evidence that biotin is concerned with fat metabolism. Gavin and McHenry[25] have obtained fatty infiltration of the liver of rats by the administration of biotin. The fatty livers were characterized by a high cholesterol content. The authors concluded that biotin does not augment the quantity of cholestoral synthesis but does increase its concentration in the liver.

IN AVES

In contrast to animals, birds are not capable of synthesizing biotin in their intestines. The deficiency syndrome may be produced by a nutritional absence alone as well as by the administration of avidin contained in egg white.[2, 35, 72] The deficiency syndrome consists almost entirely of skin changes. There is bleeding and cracking of the skin of the feet, reddening and swelling of the eyelids, loss of feathers and the appearance of a bloody scab on the mandible.[49] Cravens and his associates[9] have shown that biotin-deficient chickens produce eggs with a high proportion of chondrodystrophy, syndactyly, crooked tibia and twisted tarsus. Embryonic mortality was also higher, the peaks occurring on the third day and the last three days of incubation. Usually this picture is complicated by a perosis which many authors do not believe is due entirely to biotin deficiency, and which may be prevented by the use of small amounts of choline.[79, 36] The dermatitis may be relieved by treatment with biotin or its methyl ester.

Trager has shown that biotin deficient chicks and ducks are more susceptible to infection with Plasmodium lophurae, have higher "peak parasite numbers" and greater mortality than the controls. Older chicks, which have a higher biotin content of their tissues are less susceptible to *P. lophurae* infection than the younger ones. The biotin content of the blood rises after infection, possibly indicating the elimination of the parasite from the blood. The mechanism for this is, as yet, unknown.[93] Trager's work has been confirmed and György has reported essentially the same results with *T. lewisi* in the rat.[41]

IN HUMANS

The importance of biotin in human nutrition has received considerable attention. Findlay and Stern[22] first suggested that biotin was in some way associated with Swift's disease in children. Appel has reported that there is little difference in the total urinary biotin of normal individuals and those with a variety of diseases. The normal range for biotin in the urine in 24 hours is 14-111 mg. and in the feces for the same period, 86-191 mg. These figures are about three to six times the intake from the diet, thus indicating the synthesis of biotin.[65]

Keller[41] has noted a relationship between biotin and skin sensitivity, and Williams[10] reported a clinical case of biotin deficiency in a patient with dermatitis exfoliativa.

This patient was on a restricted diet, a large proportion of which consisted of raw eggs. Rhoads and Abels[78] failed to induce a biotin deficiency or even reduction of urinary biotin in two patients who were fed for thirty weeks sixteen to forty times the amounts of avidin necessary to bind *in vitro* the limited amounts of biotin in their diets. Peterson and his associates[74] have shown that there is always an excess of output of biotin over intake, the degree being dependent largely on the diet. The greatest excess of output over intake occurs on a low biotin intake and the least excess occurs on a high biotin intake during liver feeding.

The most definitive work on this subject has been done by Sydenstricker and co-workers.[88, 89, 90] They maintained four humans on a low vitamin diet of which 30 per cent of the total caloric intake was supplied by egg white. On this diet the subjects developed a desquamative dermatitis and pronounced pallor of the skin and mucous membranes. These symptoms appeared in approximately ten weeks. The biotin secretion in the urine diminished to almost a tenth of its normal quantity. The blood showed a diminution in hemoglobin content, red blood cells and hematocrit, in spite of theoretically adequate amounts of iron and protein in the diet. The pathological conditions were rapidly cured by the administration of 150-300 micrograms of biotin daily. Unfortunately, definite conclusions cannot be drawn from this work since the biotin used was not pure.

IN TUMORS

For many years the effects of various vitamins which are capable of exerting a powerful regulatory influence on respiration and growth have been studied in relation to tumor metabolism. The first link between biotin and cancer was described by du Vigneaud and associates. It was shown that biotin had a procarcinogenic effect on hepatomas produced in rats with the dye dimethylaminoazobenzene, more commonly known as "butter yellow."[18] Ovalle[97] substantiated this by showing that on the addition of biotin to the diet of rats receiving butter yellow and protective vitamins, half of them developed tumors. This was surprising since Kensler and co-workers[77] previously found that the inclusion of dried liver or yeast in the diet of the rats would completely nullify the effects of the dye when it was used.

In later studies du Vigneaud showed that avidin in egg white had a strong anti-carcinogenic effect. One explanation is that the egg white does not owe its protective effect solely to the avidin but is itself capable of partially detoxifying the dye.[43] Other workers[97] have since reported the biotin content of tumors to be higher than that of normal tissues. Embryonic tissue, which, in common with tumors, possesses the ability to grow rapidly, also contains relatively large quantities of biotin. West and Woglom[96] have concluded that the biotin level of tumors deviates from the normal adult values in the same direction as that of corresponding embryo tissues.

The attractive hypothesis, however, that by a reduction in the biotin supply an inhibition of tumor growth may be accomplished has not proved to be entirely true. In the work of Rhoads and Abel[78] already cited, one patient had a chronic lymphocytic leukemia and the other an inoperable cancer of the breast. No clinically evident biotin deficiency was secured and the course of the neoplasms was not altered. The patient reported by Williams[100] as having the only naturally occurring biotin deficiency on record, subsequently developed a carcinoma of the penis. By maintaining tumor-bearing mice on egg white diets West and Woglom found that the biotin content of the tumor could be markedly reduced with no great influence on the growth of the tumors.

Doubt is expressed by du Vigneaud that tumor tissue ever has a higher biotin content than normal tissues.[48] Pollock and his associates [77] determined the biotin content of a great many neoplastic and normal tissues and concluded that in all probability, cancers neither require nor are associated with a high biotin content.

More recently, an explanation has been offered for the obvious discrepancy which exists in the biotin content of tumors and

normal tissue. Burk and Wingler[4] have shown that there are substances occurring naturally in normal tissues which are chemically similar to biotin. These substances do not cure biotin deficiency in animals or combine with avidin. Thus it is possible that reports showing a higher biotin content for normal tissues may be the result of inadvertently measuring both true biotin and the animal-inactive, avidin-uncombinable biotin forms. These authors[5] state that the percentage of avidin-uncombinable biotin in normal and tumor tissues of biotin deficient rats rises to many times the normal values of 1 to 5 per cent, up to as high as 80 to 90 per cent.

In passing, it is of interest to note that biotin, in the living animal or in tissue cultures, will not affect the rate of axon growth.[6, 23]

CONCLUSION

In attempting to appraise the value of biotin to humans, one must primarily remember that a great number of investigations on this subject are still in progress, the results of which may radically change our concept of this vitamin. At present, however, one fact stands out as of paramount importance, namely, that the intestinal synthesis of biotin appears to be adequate for human needs. A natural deficiency can evidently occur only under bizarre circumstances and even an induced deficiency is difficult to produce. Therefore biotin seems to be of importance in a secondary nature only, that is in its relation to tumors. No clinical deficiency has as yet been produced in a human with a neoplasm and it would therefore be unjustifiable to attempt to draw a conclusion at the present time. It is doubtful that sub-clinical deficiency states of this vitamin exist to the degree of making disease processes, where they exist in conjunction with this state, develop into a more fulminating nature. The future of biotin appears to lie chiefly in its clinical effect on neoplasms and, what is perhaps more important, in the further investigation of related chemical substances. Of these, avidin in particular bears watching and with time it may well attain a position out of all proportion to the one it now occupies.

SUMMARY

1. Biotin is a recently isolated member of the vitamin B complex.

2. It is essential to the life and growth of some bacteria and yeasts, apparently being a co-enzyme of the respiratory metabolism.

3. The specific chemical formula and molecular structure have been determined.

4. Yeast growth assay methods are the best in use at the present time.

5. Biotin is widely distributed in nature although in minute quantities.

6. Bacteria have varying abilities of synthesizing biotin.

7. Biotin deficiency causes a specific syndrome in various animals and man.

8. Its activity is opposed by avidin, a protein constituent of egg white.

9. Bacterial synthesis of biotin in the intestinal tract is adequate for human needs.

10. The deficiency state in *Aves* increases the susceptibility to and course of malaria.

11. It may be a procarcinogenic agent.

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NEW ORLEANS
Medical and Surgical Journal
Established 1844
Published by the Louisiana State Medical Society under the jurisdiction of the following named Journal Committee:

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SUBSCRIPTION TERMS: $3.00 per year in advance, postage paid, for the United States; $3.50 per year for all foreign countries belonging to the Postal Union.

News material for publication should be received not later than the eighteenth of the month preceding publication. Orders for reprints must be sent in duplicate when returning galley proof.

Manuscripts should be addressed to the Editor-in-Chief, 1430 Tulane Ave., New Orleans, La.

THE JOURNAL *does not hold itself responsible for statements made by any contributor.*

HEALTH AND MEDICAL LEGISLATION

There has been sent out by Marjorie Shearon, Ph. D., who signs herself as Research Analyst, Conference of the Majority of the United States Senate and gives her address as Senate Office Bldg., Room 8B, two mimeographed discussions of current developments in the United States Senate. We do not know who Miss Shearon represents but we do know the material that has so far appeared is attractively prepared, most readable and decidedly in favor of the medical profession. In bulletin No. 2 Miss Shearon points out that the revised Taft-Ball-Smith Bill, the National Health Act of 1947, is now ready for introduction. This calls for the establishment of a National Health Agency which would be under the Department of Health, Welfare and Education which will have three under secretaries and eventually a Cabinet officer who will be in charge of the welfare department. She speaks of this as nothing more or less than a glorified Federal Security Agency which would be the worst possible set-up for health and medical activities. If such Cabinet position is established it seems almost sure that it will be given to a welfare official, "to a social insurance devotee, or to a welfare official, combining the social worker's viewpoint with a bias in favor of national social insurance." Miss Shearon mentions the fact that Watson B. Miller, the present Federal Security Agency Administrator, is a strong proponent of compulsory sickness insurance such as the Wagner-Murray-Dingell Bill advocates and he is a very likely candidate for the Cabinet post.

If it should come about that the welfare department should be established as a Cabinet position it would look as if this would be the end for the time being at least of a much to be hoped for Cabinet set up in which a physician would represent the various organizations which have to do with the care of the sick. This is a measure which intelligent physicians have been advocating for years but it would all go by the board if a welfare department should be established. It would not only see the passing of any immediate representation of the medical profession in the Cabinet but actually it would mean that the medical profession would probably be worse off than it is at the present time in so far as bureaucratic control of medical activities is concerned. There should be a separate health agency. Undoubtedly the American Medical Association would be in a position to combat the ideas that are represented in the Taft-Ball-Smith Bill. Nevertheless it would be wise to accept Miss Shearon's ideas for members of the medical

profession to express their views as individuals to their Representatives and Senators.

BAL

The medical profession is well acquainted with the advances that have been made in therapeusis in the past few years, notably in the management and treatment of infectious diseases. Very extensive researches are now under way or about to get under way to study the effect of antibiotics in the treatment of tuberculosis. It is rather unusual, however, to find that certain new and almost unheard of drugs have been employed in other disorders which are almost as magical in their effect as are the sulfa preparations, penicillin and streptomycin in the infectious diseases.

BAL is one of the new drugs that because of war secrecy has only recently been announced to the medical profession. BAL is an abbreviation for British Anti-Lewisite, a preparation which was developed as an antidote to arsenic blister gases. It was intended entirely for local decontamination but was found later to be extremely effective in the systemic treatment of severe arsenic poisoning. Arsenic poisoning might occur after hypothetical exposure to arsenical blister gases but the drug has been found to be of tremendous value in the treatment of the complications that result from arseno-therapy. It has also been found to have remarkably powerful protective and therapeutic value in the treatment of mercury poisoning.

The literature on BAL is very scanty but so important was it considered to put before the American medical profession the clinical uses of BAL (2, 3-dimercaptopropanol) that some fifteen articles were recently published as a supplement of the Journal of Pharmacy and Experimental Therapeutics, and in the Journal of Clinical Investigation for July practically the entire issue was devoted to experimental and clinical studies of BAL by those who were given the drug for special investigations.

The clinical reports of the use of this drug are almost unbelievable. Eighty per cent of patients with typical arsenical exfoliative dermatitis showed definite improvement within three days and were fully recovered in approximately two weeks. Of fifty-five patients with hemorrhagic encephalitis as result of intensive arsenic treatment, forty of whom were apparently on the point of death, forty-four recovered within twenty-four hours to seven days. In the more severely poisoned patients BAL was administered parenterally. The compound has been used locally but for the most part intramuscular injection is the method of choice.

A group of twenty-three patients, after a study of the drug on the treatment of experimentally produced mercury poisoning in the animal, were given BAL after ingesting bichloride of mercury in doses sufficiently large to have resulted in death in the majority of them. Actually what took place was that only one patient died.

It is quite possible that BAL may be equally beneficial both in preventing and treating poisoning from other heavy metals. The drug should be made available and should be utilized by those who are treating large groups of patients or even an occasional patient who may have syphilis. Certainly it should be in the accident room of any hospital which may be called upon to treat a patient who has taken bichloride of mercury.

MORTALITY FROM DEGENERATIVE DISEASES

It is a well known fact that death rate from infectious diseases has markedly diminished, notably in pulmonary tuberculosis, and also in the last few years since the development of new chemotherapeutic agents, in pneumonia, meningitis and other coccal diseases.

Typhoid fever and most of the bacillary diseases are well under control through public health measures to ensure a pure water supply, proper disposal of excreta and vaccination of school children. Within the last ten years there has been over a 30 per cent decrease in infant and maternal mortality. The consequence is that life ex-

pectancy has definitely increased in the last few decades. Improvement in mortality has been most pronounced in the younger age groups. In 1915 the mortality rate per 100,000 in young males was 30, now it is around 10. There has been a corresponding decrease in the death of young females.

As result of the increased age incidence of the population as a whole, one would expect and anticipate that degenerative diseases would be responsible for a goodly proportion of the deaths that take place in this country nowadays. To a certain extent this is true. Heart disease leads all other diseases as a cause of death, and the heart disease that causes the death is usually that which is dependent upon ageing. The impression is quite general among physicians that diseases of the heart, arteries and kidneys now cause as many or more deaths than they did thirty years ago, but according to the statistics of the Metropolitan Life Insurance Company there has been a marked decline in mortality in these diseases in the past three decades. The death rate from this important group of causes has dropped approximately 30 per cent. The greatest reduction in mortality from cardiovascular-renal disease has been particularly notable among the white female group. The statisticians of the Metropolitan Life Insurance Company attribute the decreases in mortality, particularly in early and middle adult life, to the absence of complications as result of childhood infections. Other causes are responsible in part as well, as for example the reduction in syphilitic heart disease as result of enlightened therapy.

It should be borne in mind that while there has been an actual decrease in the mortality rate, the true death rate from cardiovascular-renal disease is higher than it was a third of a century ago but this is before statistical correction was made for the increased average age of the population as a whole.

These figures are enlightening and instructive to the physician. From the point of view of the economist and of the legislator it is obvious that old age pensions and the payment of Governmental money to the indigent must be materially increased in the future because of the increased age of the general population.

COMMENTS ON A RECENT EDITORIAL

An editorial appearing this past fall, in discussing the work of a certain state health official, was based on certain information received through the editorial office. It is to be regretted by the editor that certain facts have lately come to his attention concerning this ex-health official that were not in accord with the information that the editor had received. The recent information would indicate that the editorial of favorable comment caused considerable discussion among the members of the Medical Society because the former health official had by no means always cooperated with organized medicine. This editorial we regret very much. The editor wishes to mention definitely that the best interests of the State Society come primarily above any and all interests affecting officers of bodies not directly associated with organized medicine.

ORGANIZATION SECTION

The Executive Committee dedicates this section to the members of the Louisiana State Medical Society, feeling that a proper discussion of salient issues will contribute to the understanding and fortification of our Society.

An informed profession should be a wise one.

1947 ANNUAL MEETING

Plans are now being made for an outstanding meeting of the State Society to be held in New Orleans May 12-14. An unusual scientific program will consist of symposia conducted by three prominent out-of-state

guests, Drs. Harry Gold, of New York, Maxwell Finland, of Boston and Raymond L. Gregory, of Galveston, and papers presented by members of the organization before general and specialty group meetings. Further details will be carried in subsequent issues of the Journal.

Members planning to attend the meeting should make hotel reservations, by communicating with the office of the Secretary-Treasurer, without delay as there are only a limited number of accommodations available.

—o—

REPORT OF COMMITTEE ON REVISION OF CHARTER; CONSTITUTION AND BY-LAWS OF LOUISIANA STATE MEDICAL SOCIETY

Following is revised copy of the Charter, Constitution and By-Laws prepared by the special committee appointed for this purpose. This is published in this issue in order to comply with provisions for amending the Charter, namely that a copy be sent to each member two months prior to the annual meeting at which time final action is to be taken. It is felt by the committee that it is wise to publish the Constitution and By-Laws so that the delegates may be familiar with the revision made in these also.

CHARTER

State of Louisiana,
Parish of Orleans,
City of New Orleans.

PREAMBLE

Be it known that on this tenth day of June, in the year of our Lord, nineteen hundred and three and of the Independence of the United States of America the one hundred and twenty-eighth, before me,

Carl C. Friedrichs, Notary Public, duly commissioned, sworn and qualified, in and for the Parish of Orleans, State of Louisiana, and in the presence of the witnesses hereinafter named and undersigned,

Personally came and appeared the persons whose names are hereunto subscribed, who severally declared that, availing themselves of the laws of this State upon that subject, they have formed and organized and by these presents do form themselves into and constitute a corporation for the objects and purposes, and under the stipulations and agreements hereinafter set forth and expressed, which they hereby adopt as their Charter, to wit:

ARTICLE I

Name

The name of said corporation shall be the "LOUISIANA STATE MEDICAL SOCIETY," and its domicile shall be the City of New Orleans.

ARTICLE II

Objects and Purposes

The objects and purposes of this corporation shall be to federate and bring into one compact organization the eligible members of the medical profession of the State of Louisiana, by the organization in the various districts and parishes of local branches known as component societies, which shall receive charters from this Society, but which shall not thereby be corporate bodies; and to unite with similar associations in other States to form the American Medical Association, with a view to the extension of medical knowledge, to the advancement of medical science; to the elevation of the standard of medical education, and to the enforcement of just medical laws; to the promotion of friendly intercourse among physicians, and to guarding and fostering their material interests, and to the enlightenment and direction of public opinion in regard to the great problems of State medicine; so that the profession shall become more capable and honorable within itself and more useful to the public in the prevention and cure of disease and in the prolonging and adding comfort to life.

ARTICLE III

Powers

Under the above entitled name, and for the purposes above expressed, the said corporation shall have power and authority to make, have and use a common seal, and the same to break, alter and amend at their pleasure, and by the name, style and title provided and declared, shall be capable in law to sue and be sued, and shall be empowered to make rules, by-laws and ordinances, and to alter, amend and change the same at pleasure,—but until so altered or amended, the regulations adopted at the last annual meeting shall be the regulations of the Society,—and to do everything needful for its good government and support. It shall be and is empowered to hold, lease, receive, purchase and convey all manner of property, both real and personal, and to mortgage and otherwise encumber the same; to borrow or lend money, issue bonds and notes, accept and receive donations, legacies and bequests; to own, publish, conduct and circulate such literature as will further its expressed purposes; to name and appoint such managers, servants and employees as its interests and convenience may require; to further these expressed objects and purposes by issuing charters as hereinbefore provided to such component societies as may be formed within the various districts and parishes of this State; and otherwise to do and

perform all acts and things requisite and necessary to carry out the objects and purposes of said corporation.

ARTICLE IV

Membership

The active members of this Society shall be the active members of the component district and parish medical societies. In parishes where no component society exists any reputable and legally registered regular physician may become an active member provided his application has been endorsed by two active members of the Society in good standing and approved by the Executive Committee. After the organization in the parish of a component society he shall become a member of such society. The liabilities of the members shall be limited to the unpaid balance due by them to the Society. Power is hereby delegated to the House of Delegates or the General Body to create any other form of membership.

ARTICLE V

Officers

The officers of this corporation shall be a President, President-elect, three Vice-Presidents, Secretary-Treasurer and Councilors, one from each congressional district, the Chairman of the House of Delegates, the Vice-Chairman of the House of Delegates and the retiring President of the Society. These officers, and the members to be presented to the Governor for appointment on the State Board of Medical Examiners, shall be elected by the House of Delegates at the annual meeting by a majority vote of the delegates present. The President, President-elect, Vice-Presidents, Chairman of the House of Delegates and the Vice-Chairman of the House of Delegates shall be elected for a term of one year, the Secretary-Treasurer for a term of not more than five years and Councilors for terms of two years each; the Councilors being divided into two groups so that as nearly as possible one-half shall be elected annually. All of the officers shall serve until their successors are elected and installed. A person shall not be elected to any office who is not in attendance upon the annual session (except he has been a faithful attendant at the annual sessions and has a valid excuse), and who has not been a member of the Society for the past two years. Vacancies due to death, resignation, or other causes, shall be filled for the unexpired term by appointment of the Executive Committee. The Executive Committee shall also recommend names to the Governor for vacancies occurring by death, resignation or other causes on the State Board of Medical Examiners between the annual session.

ARTICLE VI

Executive Committee

The powers of this Society shall be vested in an Executive Committee, which shall be composed of the President, President-elect, three Vice-Presidents, the Secretary-Treasurer, the Councilors, the Chairman and the Vice-Chairman of the House of Delegates, who shall be ex-officio members of said Committee, and the retiring President of the Society, who shall serve as a member of said Committee for one year from the date of his retirement from office. They shall hold and exercise all powers not otherwise delegated. In cases of dire emergency when it is impossible for the House of Delegates to meet in annual or special session, the Executive Committee shall assume the duties invested in the House of Delegates by this Charter, Constitution and By-Laws. They shall meet at the domicile of the Society at least twice between annual sessions at the call of the President. Special meetings must be called by the President or the Secretary-Treasurer on the written request of four members of the Executive Committee.

ARTICLE VII

Legal Representative

The President of this Society, or, in his absence, the Vice-Presidents in order, or in their absence, the Secretary-Treasurer, is hereby designated as the officer upon whom citations may be served.

ARTICLE VIII

Life of Corporation; How to Dissolve

This corporation shall exist and continue for a period of ninety-nine years, unless sooner dissolved by a two-thirds vote of the entire membership, at a meeting specially called for that purpose after thirty days' public notice. In case of such a vote dissolving this corporation, the said meeting shall, at the same time that such vote is taken, elect three liquidators to settle and wind up its affairs.

ARTICLE IX

Amendments

The Society may amend any article of this Charter by a two-thirds vote of the active members registered at any annual session, provided that such amendment shall have been presented at a meeting of the House of Delegates at the previous annual session, and that it shall have been sent officially to each member, district and parish society, at least two months before the session at which final action is to be taken, and provided that said amendment is recorded and otherwise proceeded with as required by law.

In testimony whereof, the said parties have hereunto affixed their signatures, together with me, Notary Public, and the subscribed competent witnesses, on the day and date first above written and after reading the whole.

(Original Signed):

E. D. Friedrichs,	A. W. DeRoaldes,
John J. Archinard,	Fred J. Mayer,
P. E. Archinard,	S. L. Williams,
P. W. Parham,	J. M. Barrier,

D. L. Pothier, M. D., per pro. Wm. M. Perkins
Edwin J. Graner, L. B. Arceneaux,
S. M. D. Clark, C. M. Sitman,
L. C. LeBeuf, J. F. Buquoi
C. D. Simmons, per pro. A. G. Friedrichs,
F. A. Larue, Chas. Chassaignac,
R. Matas, Homer Dupuy,
Wm. M. Perkins, Jno. B. Elliott,
E. Denegre Martin, Geo. J. Friedrichs,
J. A. Storck, per pro. A. G. Friedrichs.
Andw. G. Friedrichs,

Witnesses:
J. Blanc Monroe
Chas. F. Hester.

C. C. FRIEDRICHS,
Notary Public.

I, J. Ward Gurley, District Attorney for the Parish of Orleans, State of Louisiana, do hereby certify that I have examined the foregoing Act of Incorporation of the Louisiana State Medical Society, and am of opinion that the objects and purposes of said corporation, as specified in said act, are legal, and that none of the provisions therein contained are contrary to law.

New Orleans, La., June 5, 1903.

J. WARD GURLEY,
District Attorney for Parish of Orleans.

———o———

I, the undersigned Recorder of Mortgages, in and for the Parish of Orleans, State of Louisiana, do hereby certify that the above and foregoing Act of Incorporation of the LOUISIANA STATE MEDICAL SOCIETY, and the certificate of the District Attorney for the Parish of Orleans, was this day recorded in my office, in book 750, folio 432, June 10, 1903.

(Signed) EMILE LEONARD, D. R.

———o———

CONSTITUTION

ARTICLE I

Name of Society

The name and title of this organization shall be the LOUISIANA STATE MEDICAL SOCIETY.

ARTICLE II

Purposes of the Society

The purposes of this Society shall be to federate and bring into one compact organization the eligible members of the medical profession of the State of Louisiana and unite with similar associations in other States to form the American Medical Association, with a view to the extension of medical knowledge and to the advancement of medical science; to the elevation of the standard of medical education, and to the enactment and enforcement of just medical laws; to the promotion of friendly intercourse among physicians, and to the guarding and fostering their material interests, and to the enlightenment and direction of public opinion in regard to the great problems of State medicine; so that the profession shall become more capable and honorable within itself and more useful to the public, in the prevention and cure of disease, and in prolonging and adding comfort to life.

ARTICLE III

Component Societies

Component Societies shall consist of those District and Parish Medical Societies which hold charters from this Society.

ARTICLE IV

Composition of the Society

This Society shall consist of active, associate, honorary, inactive and intern members.

Section 1. *Active Members*—The active members of this Society shall be the active members of the component district and parish medical societies, also physicians otherwise eligible to active membership in any district or parish not having a component society; provided, that after the organization in such district or parish of a component society they shall become members of said society or forfeit membership in the State Society.

Section 2. *Associate Members*—Associate members of component societies will be eligible for associate membership; also physicians in the service of the Veterans' Bureau, Army, Navy or Public Health Service of the United States, who are on active duty and stationed in the state may be elected to associate membership when endorsed by two active members in good standing of the Society to whom they are personally known. Such membership is not to have the privileges of executive character or protection of medical defense. Dues for associate membership will be one-half amount of dues for active membership.

Section 3. *Honorary Members*—Any member in good standing who has rendered meritorious service to organized medicine or contributed to the advancement of scientific medicine, or any person not a member distinguished in medicine or the collateral branches of science may, upon recommendation of the Council, be elected to honorary membership. Active members elected to honorary membership shall have the same rights and privileges of active members but shall not be permitted to hold office. Dues and assessments of such members shall be deleted. Honorary membership in a component society does not necessarily imply honorary membership in the State Society.

Section 4. *Inactive Members*—Inactive membership shall include physicians who have been in active practice and members of long standing of the State Society who shall be approved for such membership by the Executive Committee. They shall not be entitled to medical defense nor shall

they be eligible to hold office. No dues shall be required of inactive members.

Section 5. *Intern Members*—Physicians serving internships or residencies in accredited hospitals shall during their period of internship or residency be eligible to membership in this Society through their respective component societies as intern members. They shall not be entitled to medical defense, nor shall they be eligible to hold office or vote. Dues for intern members shall be $1.00 per year.

Section 6. *Parish and District Societies*—Parish and District Societies cannot include in their membership physicians who are not members in good standing of the Louisiana State Medical Society. Component District and Parish Societies not complying with this provision shall forfeit their Charters.

ARTICLE V

Guests

Any distinguished person, medical or otherwise may become a Guest during any annual session upon invitation of the Society or its Executive Committee, and shall be accorded the privilege of participating in all of the scientific program for that session.

ARTICLE VI

Delegates

Delegates shall be those members who are elected in accordance with this Constitution and By-Laws to represent their respective component district and parish societies in the House of Delegates of this Society.

ARTICLE VII

House of Delegates

The House of Delegates shall be the legislative and business body of the Society, and shall consist of (1) delegates elected by the component district or parish societies, and (2) the officers of the Society as defined in this Constitution and (3) an Advisory Body composed of Past Presidents without the power of voting on Constitutional offices.

ARTICLE VIII

District Societies

The Executive Committee shall provide for the organization of district and parish societies for the promotion of the best interests of the profession.

ARTICLE IX

Sessions and Meetings

Section 1. The Society shall hold an annual session, during which there shall be held daily scientific and general meetings which shall be open to all registered members and guests. The time, character and number shall be determined by the Executive Committee.

Section 2. The place for holding each annual session shall be fixed by the House of Delegates. In case of emergency and a meeting can not be held at a designated place and it is impossible to hold a meeting of the House of Delegates, the Executive Committee will be empowered to alter place of meeting.

Section 3. The Executive Committee shall provide for a division of the scientific program of the Society into appropriate sections at its first meeting, which will take place not later than thirty days after the last day of the annual session, and the President shall appoint chairmen of the various sections not later than thirty days following his installation.

ARTICLE X

Officers

Section 1. The officers of this Society shall be a President, President-elect, three Vice-Presidents, a Secretary-Treasurer, and Councilors, one from each Congressional District, the Chairman and the Vice-Chairman of the House of Delegates and the retiring President of the Society.

Section 2. The President, President-elect, Vice-President, Chairman and Vice-Chairman of the House of Delegates shall be elected for a term of one year. The Secretary-Treasurer shall be elected for a term of not more than five years. The Councilors shall be elected for a term of two years each, being divided into two groups so that as nearly as possible half shall be elected for one year and the rest for two years, and thereafter each group for two years. All of these officers shall serve until their successors are elected and installed.

Section 3. The officers of this Society and the names of the members to be presented to the Governor of the State for appointment on the State Board of Medical Examiners shall be elected by the House of Delegates on the morning of the last day of the annual session, and a person shall not be elected to any office or be recommended for appointment on the State Board of Medical Examiners, who is not in attendance (except he has been a faithful attendant at the annual sessions and has a valid excuse) and who has not been a member of the Society for the past two years.

ARTICLE XI

Funds and Expenses

Funds for meeting the expenses of the Society shall be arranged for by the collection of annual dues, by voluntary contributions, assessments and public benefits, and from the sale of the publications and by any other means sanctioned by the Executive Committee and approved by the Society. Funds may be appropriated to defray the expenses of the Annual Session, for publication, and for such other purposes as will promote the welfare of the Society and profession.

ARTICLE XII

Referendum and Recall

Section 1. The General Meeting of the Society may, by a two-thirds vote, order a general referendum upon any question pending before the House of Delegates, and the House of Delegates may, by

similar vote of its own members, or after a like vote of the General Meeting, submit any such question to the membership of the Society for a final vote; and if the persons voting shall comprise a majority of all the members present, a majority of such vote shall determine the question, and be binding upon the House of Delegates.

Section 2. Any officer neglecting his duty or violating any article of this Charter, Constitution or By-Laws may be removed from his office after due trial at any regular or special session of the House of Delegates, provided thirty days' notice be furnished in writing to the officer so charged. The charges should originate in the Council either directly or by the request of twenty-five active members in good standing.

ARTICLE XIII

The Seal

The Society shall have a common seal, with power to break, change or renew the same at pleasure.

ARTICLE XIV

Amendments

The House of Delegates may amend any article of this Constitution by a two-thirds vote of the delegates registered at that annual session, provided that such amendments shall have been presented at a previous annual meeting and have been approved by the House of Delegates.

BY-LAWS

CHAPTER I

Membership

Section 1. *Privileges*—All members in good standing shall be privileged to attend all meetings and take part in all proceedings of the annual session, but only active members shall be eligible to any office within the gift of the Society.

Section 2. *Rights*—The name of a physician upon the properly certified roster of members of a component district or parish shall be prima facie evidence of his right to register at the annual sessions of this Society provided his State Society dues have been received for the current year.

Section 3. *Suspension or Expulsion*—No person who is under sentence of suspension or expulsion from any component society of this Society, or whose name has been dropped from its roll of members, shall be entitled to any of the rights or benefits of this Society, nor shall he be permitted to take any part in any of its proceedings until such time as he has been relieved of such disability.

Section 4. *Registration*—Each member in good standing in attendance at the annual session shall, after registering, receive a badge which shall be evidence of his right to all privileges of membership at that session. No member or delegate shall take part in any of the proceedings of an annual session until he has complied with the provisions of this section.

CHAPTER II

Annual and Special Sessions of the Society

Section 1. *Annual Sessions*—The Society shall hold an annual session at such time and place as has been fixed at the preceding annual session or as fixed by this Constitution and By-Laws. At this annual session shall be held general, installation and scientific meetings and the annual meeting of the House of Delegates.

Section 2. *Special Sessions*—Special sessions of either the Society or House of Delegates shall be called by the President at his discretion or by petition of twenty-five active members.

Section 3. *Meetings*—The *General Meetings* shall include all registered active members who shall have equal rights to participate in the proceedings and discussions and to vote on pending questions. These meetings shall be for the purpose of considering matters affecting the welfare of the Society and the profession. The entire time of the session shall be devoted to business of interest to the Society and the profession. Each General Meeting shall be presided over by the President, or in his absence or disability, or by his request, by one of the Vice-Presidents. A general meeting shall be called at the conclusion of the annual session of the House of Delegates for the purpose of considering the report of the House of Delegates. The General Meeting shall have authority to create committees or commissions for scientific investigation of special interest and importance to the profession and public, and to receive and dispose of reports of the same; but any expense in connection therewith must first be approved by the House of Delegates.

An *Installation Meeting* shall be held during the annual session. The nature of this meeting shall be left to the discretion of the Chairman of the Committee on Arrangements. At this meeting the reports of the retiring president and the address of the incoming president, and the annual oration man be rendered.

The *Scientific Meetings* shall be devoted to papers and discussions relating to scientific medicine, arranged by the Committee on Scientific Work. The scientific program of each meeting shall be divided into two principal sub-divisions, namely, Medicine and its allied branches, and Surgery and its allied branches. These two main sub-divisions shall be further sub-divided into sections, each section having a specified number of papers, as follows:

Medicine and Allied Branches

Medicine and Therapeutics	7
Pediatrics	3
Nervous Diseases	3
Bacteriology and Pathology	3
Public Health and Sanitation	5

Gastro-enterology	2
	(23)
Surgery and Allied Branches:	
General Surgery (Including Dermatology)	7
Gynecology and Obstetrics	4
Eye, Ear, Nose and Throat, Including Stomatology	5
Urology	2
Radiology	3
Orthopedic Surgery	2
	(23)

The order of exercises, papers and discussions as set forth in the official program shall be followed from day to day until it has been completed; but the papers of one session shall not encroach upon the papers of another session. No address or paper before the Society, except those of the President and orators, shall occupy more than fifteen minutes in its delivery; and no member shall offer discussion longer than five minutes, nor more than once on any subject. All papers read before the Society shall be its property. Each paper shall be deposited with the Secretary-Treasurer when read, and if this is not done the author shall not be allowed to read a paper at the two next succeeding Annual Meetings. Each paper shall be read by its author. If this condition is not complied with the author shall not be allowed to read a paper at the two next succeeding Annual Meetings. Any author failing to read his paper at any Annual Meeting shall not be allowed to read a paper at the two next succeeding Annual Meetings. If any author shows his good intent by forwarding his paper to the Secretary-Treasurer in time for the Annual Session, he shall not suffer this penalty. Any author suffering any of the above penalties shall also not be allowed to appear on the official program in the capacity of opening discussions for a like time. No member shall present more than one paper at any Annual Meeting.

The House of Delegates shall meet annually at the time and place of the Annual Session of the Society.

CHAPTER III

Installation of President

The President-elect shall be installed as President during the annual session, the time and place to be left to the discretion of the Chairman of the Committee on Arrangements. In the event that a scheduled annual session can not be held the Executive Committee shall determine time and place for installation.

CHAPTER IV

House of Delegates

Section 1. *Meetings*—The House of Delegates shall so fix its hours of meeting as not to conflict with the General Meeting of the Society, or with the meeting held for the address of the President and the annual oration, and so as to give delegates an opportunity to attend the other scientific proceedings and discussions so far as is consistent with their duties. The House of Delegates shall meet on the morning of the day previous to the Annual Meeting, and it may remain in session up to the final adjournment of the General Meeting. On the morning of the last day of the session the House of Delegates shall elect its Chairman and Vice-Chairman for the ensuing year.

Section 2. *Number of Delegates from Each Component Society*—Each Component Society shall be entitled to send to the House of Delegates each year one delegate for every twenty-five active members, and one for each fraction thereof, but each District and Parish Society holding a charter from this Society, which has made its annual report shall be entitled to its representation. Each district society shall be entitled to only one delegate.

Section 3. *Quorum*—A majority of the registered delegates shall constitute a quorum, and all of the meetings of the House of Delegates shall be open to members of the Society.

Section 4. *Aims and Purposes*—It shall, through its officers, Executive Committee and otherwise, give diligent attention to and foster the scientific work and spirit of the Society, and shall constantly study and strive to make each Annual Session a stepping stone to future ones of higher interest. It shall consider and advise as to the material interests of the profession, and of the public in those important matters wherein it is dependent upon the profession, and shall use its influence to secure and enforce all proper medical and public health legislation, and to diffuse popular information in relation thereto. It shall make careful inquiry into the condition of the profession of each parish of the State, and shall have authority to adopt such methods as may be deemed most efficient for building up and increasing the interest in such parish societies as already exist, and for organizing the profession in parishes where societies do not exist. It shall encourage postgraduate work in medical centers, as well as home study and research, and shall endeavor to have the results of the same utilized and intelligently discussed in the component societies.

Section 5. *Delegates to A. M. A.*—It shall elect representatives to the House of Delegates of the American Medical Association in accordance with the Constitution and By-Laws of that body in such a manner that not more than one-half of the delegates shall be elected in any one year, when possible.

Section 6. *Charters*—It shall, upon application, provide and issue charters to district and parish societies organized to conform to the spirit of this Constitution and By-Laws.

Section 7. *Organization*—In sparsely settled sections it shall have authority to organize the physicians of two or more parishes into societies to be

designated by hyphenating the names of two or more parishes so as to distinguish them from district and other classes of societies, and these societies, when organized and chartered, shall be entitled to all the privileges and representation provided herein for parish societies until such parishes may be organized.

Section 8. *District Societies*—In extraordinary cases it may form district societies of groups of parishes or parts of parishes for the purpose of fostering the scientific interest of the members, but this is not in any sense to be construed as interfering in organizing the various parishes into component societies for the purpose of representation in the House of Delegates.

Section 9. *Committees*—It shall have authority to appoint committees for special purposes from among members of the Society who are not members of the House of Delegates, and such committees may report to the House of Delegates in person, and may participate in the debate thereon.

Section 10. *Memorials and Resolutions*—It shall approve all memorials and resolutions issued in the name of the Society before the same shall become effective.

Section 11. *Publication of Proceedings*—It shall present a summary of its proceedings to the last General Meeting of each Annual Session, and publish the same in the Transactions or Offical Journal.

CHAPTER V

Fiscal Year

The Fiscal year of the Society shall begin January first.

CHAPTER VI

Election of Officers

Section 1. Nominations shall be made in open meeting of the House of Delegates on the first day of its meeting and the election made by secret ballot on the last day, and a majority of the votes cast shall be necessary to elect.

Section 2. *Dual Office-Holding*—No member may hold two elective offices simultaneously except those elected to standing committees.

CHAPTER VII

Duties of Officers

Section 1. *President*—The President shall preside at all meetings of the Society; shall appoint all committees not otherwise provided for; shall deliver an annual address at such time as may be arranged; shall give a deciding vote in case of a tie, and shall perform such other duties as custom and parliamentary usage may require. He shall be the real head of the profession in the State during his term of office, and, as far as practicable, shall visit by appointment the various sections of the State and assist the Councilors in building up the district and parish societies, and in making their work more practical and useful.

Section 2. *Vice-Presidents*—The Vice-Presidents shall assist the President in the discharge of his duties.

Section 3. *President-elect*—The President-elect shall familiarize himself with the affairs of the Society, keeping in touch with the organization, and shall assume the duties of President upon his installation.

Section 4. *Chairman of House of Delegates*—The Chairman of the House of Delegates shall preside at meetings of the House of Delegates and shall perform such duties as custom and parliamentary usage require.

Section 5. *Vice-Chairman of House of Delegates*—The Vice-Chairman of the House of Delegates shall officiate for the Chairman in his absence or at his request.

Section 6. *Secretary-Treasurer*—The Secretary-Treasurer, as Chairman of the Committee on Scientific Work, shall prepare and issue the programs for and attend all meetings of the Society, and he shall keep minutes of their respective proceedings in separate record books. He shall be custodian of all record books and papers belonging to the Society. He shall provide for the registration of the members and delegates at the Annual Session. He shall keep a card index register of all the legal practitioners of the State by parishes, noting on each his status in relation to his society, and upon request shall transmit a copy of this list to the American Medical Association for publication. In so far as it is in his power he shall use the printed matter, correspondence and influence of his office to aid the Councilors in the organization and improvement of the parish societies, and in the extension of the power and usefulness of this Society. He shall conduct the official correspondence, notifying members of meetings, officers of their election and committees of their appointment and duties. The Secretary-Treasurer shall give bond for the trust reposed in him as fixed by the Executive Committee. He shall demand and receive all funds due the Society, together with the bequests and donations. He shall, in general, have the care and management of the fiscal affairs of the Society. He shall be allowed to draw checks for the purpose of meeting and paying of the routine expenses of the Society without vouchers from the President, provided such amounts shall not be in excess of the amount specified by the Budget and Finance Committee; he shall submit the books of the Society to such examinations as the House of Delegates may order, and he shall at the first session of the annual meeting of the House of Delegates render an account of his activities and of the financial status of the organization. He shall collect and enter upon the books the annual dues for members and perform such other duties as may pertain to his office. In order that the Secretary-

Treasurer may be enabled to give that amount of time to his duties which will permit of his becoming proficient, it is desirable that he should receive compensation. The amount of salary shall be fixed by the Executive Committee within limits fixed by Budget and Finance Committee.

CHAPTER VIII

Council

Section 1. *Meetings*—The Council shall hold meetings during the Annual Session of the Society at such times as necessity may require, subject to the call of the Chairman or on petition of three Councilors. It shall meet on the date of the first meeting of the Executive Committee after the Annual meeting of the House of Delegates for reorganization and for the outlining of work for the ensuing year. At this meeting it shall elect a Chairman and Secretary and it shall keep a permanent record of its proceedings. It shall, through its Chairman, make an annual report to the House of Delegates at such time as may be provided.

Section 2. *Duties of Councilors*—Each Councilor shall be the organizer, peacemaker and censor for his district. He shall visit each parish in his district at least once a year for the purpose of organizing component societies where none exist, for inquiring into the condition of the profession, and for improving and increasing the zeal of the parish societies and their members. He shall make a report including activities of the component societies in his district, and of the condition of the profession of each parish in his district, to each Annual Session of the House of Delegates. The necessary traveling expenses incurred by such Councilor in the line of the duties herein imposed may be allowed by the House of Delegates upon a proper itemized statement, but this shall not be construed to include his expense in attending the Annual Session of the Society.

Section 3. *Duties of Council*—Collectively the Council shall be the Board of Censors of the Society. It shall consider all questions involving the rights and standing of members, whether in relation to other members, to the component societies, or to this Society. All questions of an ethical nature brought before the House of Delegates or the General Meeting shall be referred to the Council without discussion. It shall hear and decide all questions of discipline affecting the conduct of members or of a district or parish society, upon which an appeal is taken from the decision of an individual Councilor. Its decision in all such cases shall be final.

Section 4. *Rights*—The Council shall have the right to communicate the view of the profession and of the Society in regard to health, sanitation and other important matters to the public and the lay press. Such communications shall be officially signed by the Chairman and Secretary of the Council as such. Councilors shall be ex-officio members of the House of Delegates.

Section 5. *Reports*—If a Councilor fails to have a written report of his Councilor District at the Annual Meeting, his position shall be declared vacant, if so decided by a majority vote of the House of Delegates.

CHAPTER IX

Committees

Standing Committees shall be as follows:
Committee on Arrangement
Committee on Budget and Finance
Committee on Congressional Matters
Committee on Journal
Committee on Maternal Welfare
Committee on Medical Defense
Committee on Medical Education
Committee on Medical Testimony
Committee on Public Policy and Legislation
Committee on Scientific Work

Such committees shall be elected by the House of Delegates unless otherwise provided.

Section 1. *Committee on Arrangement*—The Committee on Arrangement shall consist of the component society in the area in which the Annual Session is to be held. It shall, by committees of its own selection, provide suitable accommodations for the meeting places of the Society and of the House of Delegates, and of their respective committees, and shall have general charge of all the arrangements. Its Chairman shall report an outline of the arrangements to the Secretary-Treasurer for publication in the program and Official Journal, and both shall make additional announcements during the session as occasion may require.

Section 2. *Committee on Budget and Finance*—A Committee on Budget and Finance, whose duty shall be to present a budget of income and expense for the ensuing year. It also shall audit the books of the Secretary-Treasurer and of all committee funds and perform such advisory duties as may be of benefit to the Society, and shall make its report to the Executive Committee at the first meeting and also to the House of Delegates. It shall consist of three members, appointed by the Chairman of the House of Delegates, with overlapping terms of three years. At its discretion the services of an accredited public accountant may be employed.

Section 3. *Committee on Congressional Matters*—The Committee on Congressional Matters shall consist of three members, appointed by the President for a term of one year. The duties of this committee shall be to keep in touch with congressional bills and legislative matters which pertain to medicine and public health and inform members of the Society concerning status of same.

Section 4. *Committee on Journal*—The Journal Committee shall consist of five members with overlapping terms of three years. At the expiration of

the respective terms their successors shall be elected by the House of Delegates each for a term of three years. In the event of a vacancy occurring by resignation, death or other causes, the President shall appoint successors to serve until the next meeting of this Society, successors being then elected by the House of Delegates. The Journal Committee shall have full control of the editing and publishing of the New Orleans Medical and Surgical Journal. The State Society shall pay the Journal seventy-five cents ($0.75) per year per member in consideration of which each member shall receive the Journal for one year. The Journal Committee shall have charge of the publication of transactions, papers, and other matters.

Section 5. *Committee on Maternal Welfare*—The Committee on Maternal Welfare shall consist of eight members appointed by the President, one from each Congressional District. They shall consider all matters pertaining to maternal and child welfare which concern the public, members of this Society and the State health department. They shall cooperate with various agencies concerned with this work and determine policies for the benefit of the public and of the medical profession.

Section 6. *Committee on Medical Defense*—The administration of Medical Defense of this Society shall be entrusted to a standing committee of three members with overlapping terms to be elected by the House of Delegates; one member to be elected at each annual session for a term of three years. This committee shall have full authority governing all matters pertaining to the Medical Defense of this Society; with power to employ counsel, summon and employ expert witnesses and incur such other expenses as in the judgment of the committee may be necessary in the defense of members against whom suits may be brought; provided, always, that the total expenditure of any single suit shall not exceed 25 per cent of the fund available at the time suit is incurred. The Medical Defense Committee shall make an annual report to the House of Delegates of the cases in which it has been of service to members, and furnish an account of money received and expended, such report to be published in the official journal of the Louisiana State Medical Society at the time and in the manner that reports of other committees of the Society are published. The financial report of the Committee shall be submitted to and approved by the Committee on Budget and Finance. Each member of the Committee on Medical Defense of this Society shall be entitled to an honorarium of $10.00 per diem with traveling expenses, if required to go out of town in the investigation of any case or in attendance at court, and these same fees shall be allowed to expert witnesses under similar circumstances. The Committee on Medical Defense shall have power to adopt such other rules, not in conflict with the foregoing, as in their judgment may seem necessary until the next Annual Meeting of the House of Delegates, when such rules shall take the regular course of amendments.

Section 7. *Committee on Medical Education*—A Committee on Medical Education consisting of three members appointed by the President with overlapping terms of three years, whose duty shall be to furnish a report to the House of Delegates upon the status of medical education in the State, and to work in accordance with the Council on Medical Education and Hospitals of the American Medical Association. This appointment shall be made not later than thirty days after the last day of the Annual Session.

Section 8. *Committee on Medical Testimony*—The Committee on Medical Testimony shall consist of five members appointed by the President with overlapping terms of three years. They shall make recommendations for the improvement of expert testimony by the medical profession in accordance with legal regulations. They shall be empowered to investigate all complaints relative to violations in medical or expert testimony and to submit recommendations for improvement of legislation governing expert testimony.

Section 9. *Committee on Public Policy and Legislation*—The Committee on Public Policy and Legislation shall consist of three members and the President and Secretary-Treasurer. Under the direction of the House of Delegates it shall represent the Society in securing and endorsing legislation in the interest of the public health and of scientific medicine. It shall keep in touch with professional and public opinion, shall endeavor to shape legislation so as to secure the best results for the whole people, and shall utilize every organized influence of the profession to promote the general influence in local, State and National affairs and elections. Its work shall be done with the dignity becoming a great profession and with that wisdom which will make effective its power and influence. It shall have authority to be heard before the entire Society upon questions of great concern at such time as may be arranged during the Annual Session. The President shall have power to enlarge the Committee as exigency requires.

Section 10. *Committee on Scientific Work*—The Committee on Scientific Work shall consist of three members, of which the Secretary-Treasurer shall be Chairman, and shall determine the character and scope of the scientific proceedings of the Society for each session, subject to the approval of the Executive Committee. Early in January it shall publish in the official Journal the names of the Chairmen of Sections. The Chairman of each Section shall present the complete program of his Section to this Committee not later than 60 days previous to the Annual Session. Two weeks previous to each Annual Session it shall issue a program announcing the order in which papers, dis-

cussion and other business shall be presented, which shall be adhered to by the Society as nearly as practicable.

CHAPTER X

Medical Defense

Section 1. Active members of the Louisiana State Medical Society who have paid all dues, assessments and other charges assessed or levied by the Louisiana State Medical Society, shall be entitled, on conditions hereinafter specified, to receive without personal expense therefor, legal advice and court service of an attorney or attorneys at law in the employ of the Society, or others selected by the Committee on Medical Defense, in consultation with the defendant; and witness fees for the purpose of conducting their defense in any courts of the State in which the suit may be filed or threatened to be filed.

Section 2. Fifty cents per capita shall be set aside as a special fund for Medical Defense. Whenever such fund shall exceed the sum of $20,000, the surplus over and above this amount may be used for such other purposes as the House of Delegates may direct.

Section 3. The liability of this Society shall include in Medical Defense only the expenses necessary for the legal defense of its members and not damages awarded.

Section 4. The Society shall not undertake the defense of a member in a suit that may be brought to secure indemnity for service rendered prior to January 1, 1914, nor in any case in which the member who applies for medical defense by the Society, has failed to pay his annual dues for 1914 or prior to the rendering of services which are the basis of the suit; and medical defense by the Society shall not be available to those who are delinquent or to those who have not paid the annual dues of the Society prior to the rendering of services for which indemnity is asked.

Section 5. A member desiring to avail himself of the services of the Committee on Medical Defense in connection with litigation brought or threatened must first submit to a local committee of his parish medical society—to be composed of the President, Secretary and one other member in good standing, who may be nominated by the defendant—a full statement of the question at issue, including the diagnosis and treatment of the case and the names of physicians, nurses and other persons having knowledge of the same, who may be summoned as witnesses.

Section 6. The committee of the parish medical society shall immediately, after an investigation of all the circumstances and facts, transmit its report, with recommendations, to the Committee on Medical Defense of this Society.

Section 7. Accompanying such report from the parish society, if favoring medical defense by the Society, there must also be furnished the written authority of the defendant granting to the Medical Defense Committee of this Society full power to act in his behalf, and an agreement that his case shall not be compromised or settled without the consent of a majority of the Committee on Medical Defense.

Section 8. In the event that the parish committee shall fail to recommend the case as one worthy of the recognition of this Society, a direct appeal may be made to the Committee on Medical Defense of this Society, whose decision shall be final.

Section 9. Suits brought against the estate of a deceased member shall be defended as if that member were alive; provided, that such member was in good standing in the Society at the time of his death and that services for which indemnity is asked were rendered while the deceased was a member in good standing.

Section 10. The defense promised in Chapter X shall apply when the suit is brought by the patient, by the nurse or anyone who claims to have been injured by an act of the doctor at the time the doctor was in the actual performance of his professional duty.

CHAPTER XI

Assessments and Expenditures

Section 1. *Assessments and How Payable*—Each active member shall pay into the Society an annual assessment of twenty-five ($25.00), which shall constitute his membership dues. Those specifically exempted in the Constitution shall not be liable for this assessment. Intern members shall pay the sum of one dollar ($1.00) per annum. Of the amount collected from active members, one dollar ($1.00) per capita shall be set aside as an annual entertainment fund. In addition, one half dollar (50c) per capita shall be paid from the dues collected from active members into the Medical Defense Fund, one dollar ($1.00) into the Indigent Physicians Fund and one half dollar (50c) into the fund of the Committee on Public Policy and Legislation. After the first day of July and before the first day of October new active members shall pay one-half of the annual dues for the fiscal year; after the first day of October of the current year new members admitted to the Society shall pay one-quarter of the annual dues for the fiscal year.

Section 2. Component societies having a classification of Intern Membership shall pay dues to the State Society for each member in the amount of one dollar ($1.00) per annum.

Section 3. Dues must be paid in advance. The Secretary of each component society must forward to the Secretary-Treasurer of the State Society the dues and assessments of each member of his Society.

Section 4. *Delinquencies*—If dues and assess-

ments are not paid by the date of the annual meeting a member shall be suspended. Suspended members shall not be eligible to benefits.

Section 5. Physicians in organized parishes with the proper qualifications can send their dues direct to the State Society when the Parish Society in which parish they reside becomes inactive.

Section 6. *Mode of Appropriating Money*—All motions or resolutions appropriating money shall specify a definite amount, or so much thereof as may be necessary for the purpose indicated, and must be endorsed by the Budget and Finance Committee and submitted to the House of Delegates for approval.

CHAPTER XII

Travel Expense

Travel expense of members of the Executive Committee to meetings of that committee; expense of delegates to meetings of the House of Delegates of the American Medical Association; and expense of members on approved committee assignments, shall be paid from the general fund upon receipt of statement of expenditure.

CHAPTER XIII

Rules of Conduct

The principles set forth in the Code of Ethics of the American Medical Association shall govern the conduct of members in their relation to each other and to the public.

CHAPTER XIV

Rules of Order

The deliberations of this Society shall be governed by parliamentary usage as contained in Robert's Rules of Order, unless otherwise determined by a vote of its respective bodies.

CHAPTER XV

Parish Societies

Section 1. *How Created*—All parish societies now in affiliation with the State Society or those that may hereafter be organized in this State, which have adopted principles of organization not in conflict with this Constitution and By-Laws, shall, upon application to the Executive Committee, receive a charter from and become a component part of this Society.

Section 2. *Mode of Organization*—As rapidly as can be done after the adoption of this Constitution and By-Laws, a medical society shall be organized in every parish in the State in which no component society exists, and charters shall be issued thereto.

Section 3. *Charters*—Charters shall be issued only upon approval of the Executive Committee and shall be signed by the President and Secretary-Treasurer, Chairman of the Council and the Councilor of the district. The Executive Committee shall have authority to revoke the charter of any component district or parish society whose actions are in conflict with the letter or spirit of this Constitution and By-Laws.

Section 4. *Only One Charter to Each Parish Permitted*—Only one component medical society shall be chartered in any parish. Where more than one parish society exists, friendly overtures and concessions shall be made, with the aid of the Councilor of the District, if necessary, and all of the members brought into one organization. In case of failure to unite, an appeal may be made to the Council, which shall decide what action shall be taken.

Section 5. *Qualifications of Members*—Each parish society shall judge of the qualifications of its own members, but, as such societies are the only portals to this Society, and to the American Medical Association, every reputable and legally registered physician who is practicing, or who will agree to practice non-sectarian medicine, shall be eligible for membership. Before a charter is issued to any parish society, full and ample notice and opportunity shall be given to every such physician in the parish to become a member.

Section 6. *Right of Appeal*—Any physician who may feel aggrieved by the action of the society of his parish in refusing him membership or in suspending or expelling him, shall have the right of appeal to the Council and to the House of Delegates.

Section 7. *Hearing of Appeals by Council*—In hearing appeals the Council may admit oral or written evidence as in its judgment will best and most fairly present the facts, but in the case of every appeal, both as a Board and as individual Councilors in district and parish work, efforts at conciliation and compromise shall precede all such hearings.

Section 8. *Transfer of Membership*—When a member in good standing in a component society moves to another parish in this State, his name, upon request, shall be transferred without cost to the roster of the parish society into whose jurisdiction he moves, subject to the rules governing such society.

Section 9. *Choice of Membership*—A physician living on or near a parish line may hold his membership in that parish most convenient for him to attend, on permission of the society in whose jurisdiction he resides.

Section 10. *Rights of Component Societies*—Each parish society shall have general direction of the affairs of the profession in the parish, and its influence shall be constantly exerted for bettering the scientific, moral and material condition of every physician in the parish; and scientific efforts shall be made by each member, and by the society as a whole, to increase the membership until it embraces every qualified physician in the parish. In any unorganized parish in which there are ten or more

members of the State Society, these members must effect organization or forfeit their membership in the State Society.

Section 11. *Meetings*—Frequent meetings shall be encouraged, and the most attractive programs arranged that are possible. The younger members shall be especially encouraged to do postgraduate and original research work, and to give the Society the first benefit of such labors.

Section 12. *Delegates*—At some meeting in advance of the fiscal year of this Society each parish society shall elect a delegate or delegates, and alternate or alternates, to represent it in the House of Delegates of this Society, in the proportion of one delegate and alternate to each twenty-five active members, or fraction thereof, and the secretary of the society shall send a list of such delegates and alternates to the Secretary-Treasurer of this Society. Should any delegate or alternate so elected to represent any parish society fail to attend any meeting, it shall be the duty of the president of such parish medical society, or in his absence, the vice-president thereof, to appoint an alternate or alternates in writing or by telegraph. Component societies failing to comply with this provision shall be denied representation in the House of Delegates, unless otherwise decided by a two-thirds majority of delegates at meeting when a request for different action is made.

Section 13. *Duties of Secretaries of Component Societies*—The secretary of each parish society shall keep a roster of its members, and a list of the non-affiliated registered physicians of the parish, in which shall be shown the full name, address, college and date of license to practice in this State, and such other information as may be deemed necessary. He shall furnish an official report containing such information upon blanks supplied him for the purpose, to the Secretary of this Society. In keeping such roster the secretary shall note any changes in the personnel of the profession by death, or by removal to or from the parish, and in making his annual report he shall be certain to account for every physician who has lived in the parish during the year.

CHAPTER XVI

Amendments

These By-Laws may be amended at any Annual Session by a majority vote of all the delegates present at that session, after the amendment has laid upon the table one day or by unanimous consent. A copy printed on gummed paper should be mailed to each member within sixty (60) days of its enactment.

TRANSACTIONS OF ORLEANS PARISH MEDICAL SOCIETY

NEWS ITEMS

The 1943 medical records prize was awarded to Dr. W. D. Beacham at the American College of Surgeons meeting recently held in Cleveland.

Drs. Wm. H. Gillentine and Thomas Benton Sellers were guest speakers at the meeting of the South Mississippi Medical Society on December 12 at Hattiesburg. Dr. Gillentine spoke on "Cure of Heart Disease" and Dr. Sellers on "Management of the Displaced Uterus".

Dr. Howard Mahorner attended the meeting of tre Southern Surgical Association in Hot Springs, Va., December 10-12.

At the November meeting of the EENT section of the Charity Hospitay Visiting Staff the following scientific program was presented:

Presentation of Interesting Eye Cases by Dr. Charles Bahn.

Relation of Poliomyelitis and ENT Conditions by Dr. Branch J. Aymond.

Dr. F. L. Jaubert was recently re-elected president of the Louisiana Society for Crippled Children.

Dr. Henry D. Ogden attended the third annual meeting of the American Academy of Allergy in New York, November 25-27. A paper on "Severe Allergic Reactions During Cystoscopy" was prepared by Drs. Ogden, Harry L. Zengel, Jr., and John F. Lally for presentation at the meeting.

Dr. John M. Whitney was elected secretary of the Southern Branch of the American Public Health Association at their meeting in Miami recently.

Dr. Edwin L. Zander was recently elected a member of the board of directors of the New Orleans Kiwanis Club.

HOSPITAL NEWS

At a recent meeting of the Medical Advisory Committee to the Charity Hospital Staff Dr. Edwin L. Zander was elected president. Other officers elected were as follows: Dr. E. Garland Walls, vice-president; Dr. N. Polmer, secretary; Drs. Edgar Hull, John Oakley, N. J. Tessitore and Julius Lane Wilson, members of the Committee.

Dr. N. J. Tessitore was elected chairman; Drs. Edgar Hull and E. Garland Walls, members of the Qualifications Committee of the Charity Hospital.

Physicians elected to the Medical Division of the Charity Hospital Visiting Staff are as follows: Dr. Wm. A. Sodeman, chairman; Dr. Edwin S. Kagy, vice-chairman; and Dr. Joseph W. Wells, secretary.

Newly elected members of the Surgical Division of the Charity Hospital Visiting Staff are as follows: Dr. Frank Loria, chairman; Dr. Daniel W. Goldman, vice-chairman; and Dr. Edward Nelson, secretary.

Physicians elected to the sectional sections of the Charity Hospital Visiting Staff are as follows:

Surgery—Dr. L. J. O'Neil, chairman; Dr. Alex Powe, vice-chairman; and Dr. M. L. Stadiem, secretary.

Ob.-Gyn.—Dr. Conrad Collins, chairman; Dr. D. W. Goldman, vice-chairman; and Dr. Claude Callendar.

E. E. N. T.—Dr. Charles A. Bahn, chairman; Dr. Paul Lastrapes, secretary.

Urology—Dr. John G. Pratt, chairman; Dr. R. J. Mailhes, vice-chairman; and Dr. John G. Menville, secretary.

Orthopedic—Dr. Harry Morris, chairman; Dr. Irvin Cahen, vice-chairman; and Dr. A. R. Altenberg, secretary.

LOUISIANA STATE MEDICAL SOCIETY NEWS

CALENDAR

PARISH AND DISTRICT MEDICAL SOCIETY MEETINGS

Society	Date	Place
East Baton Rouge	Second Wednesday of every month	Baton Rouge
Morehouse	Second Tuesday of every month	Bastrop
Orleans	Second Monday of every month	New Orleans
Ouachita	First Thursday of very month	Monroe
Rapides	First Monday of every month	Alexandria
Sabine	First Wednesday of every month	
Second District	Third Thursday of every month	
Shreveport	First Tuesday of every month	Shreveport
Vernon	First Thursday of every month	

IMPORTANT

There is urgent need in the office of the Journal for additional copies of the November, 1946 issue. We would ask members of the State Society to forward their copies to us when they are through with them.

RAPIDES PARISH MEDICAL SOCIETY

The following is a list of the officers elected by the Rapides Parish Medical Society for 1947.

Dr. H. P. Forsythe, President, Alexandria, La.

Dr. H. C. Gahagan, 1st Vice President, Alexandria, La.

Dr. Morris Hair, 2nd Vice President, Lecompte, La.

Dr. John S. Rozier, Secretary-Treasurer, Alexandria, La.

Board of Censors: Dr. H. Aubrey White, Alexandria, La.

House of Delegates: Dr. M. B. Pearce, Alexandria, La. Alternate: Dr. H. A. White, Alexandria, La.

John S. Rozier, M. D.,
Secretary-Treasurer.

NATIONAL CONFERENCE ON MEDICAL SERVICE

There will be held in Chicago on Sunday, February 9, the 20th Annual Meeting of the National Conference on Medical Service. This will be an all-day session which will be opened by the address of the President, Dr. Cleon A. Nafe of Indianapolis. There will be a list of distinguished speakers at the morning session and the afternoon session will be devoted to a forum which will discuss a variety of subjects having to do with medical service.

AMERICAN COLLEGE OF SURGEONS

The following surgeons were recently received into fellowship in the American College of Surgeons at their convocation in Cleveland: Peachy R. Gilmer, Shreveport; William A. K. Seale, Sulphur; Gilbert C. Tomskey, New Orleans; Donald B. Williams, Lafayette.

DR. DESANCTIS SPEAKS

The exercises celebrating the completion of the new Hotel Dieu Pediatric Department included two addresses by Dr. Adolph G. DeSanctis, Director of the Department of Pediatrics of the New York Post-Graduate Medical School. Dr. Socola is chairman of the Arrangement Committee for these exercises.

A. O. A. ELECTIONS

The Tulane School of Medicine chapter of Alpha

Omega Alpha, national honorary medical fraternity, has elected 12 new members.

Seniors chosen include Hurst Bunn Hatch, Jr., Raleigh, N. C.; Erwin Hecker, Washington, D. C.; James Gentry Moore, Amarillo, Tex.; Takeshi Okano, Hawaii; Benjamin Reid Clanton, Lancaster, S. C.; George Wylie Wyatt, Amarillo, Tex.; Francis Leon Jaubert, Jr., and Aynaud Maurice Hebert, New Orleans; William Dennis Thames, Jr., Luskin, Tex.; and Thomas Everett Strain, Jr., Shreveport.

Juniors elected are Miss Flora Finch, McComb, Miss., and Francis Meredith Parks, New Orleans.

THE SCHERING AWARD

It is a pleasure to report that Mr. Stonewall B. Stickney of Tulane University School of Medicine received the third prize, a check for $200, for his contribution to the Schering Contest. It is interesting to know that in addition to the first three prizes 44 other contestants received "honorable mention" and were awarded stethoscopes.

U. S. P. H. S. NEWS

The U. S. Public Health Service will hold an examination in New Orleans March 17 at the Marine Hospital for candidates to the commissioned corps of this organization.

The Health and Hospital Division of the governor of Louisiana has been designated by the U. S. Public Health Service to administer the new Hospital Program. Hospitals and professional groups wishing to participate in the Program should direct their inquiries to Mr. Charles Mitchell, Baton Rouge, Director of the Health and Hospital Division.

TOURO INFIRMARY

The annual meeting of the Medical Staff of Touro Infirmary was held on Wednesday, January 8 at 8 p. m. The Department of Pathology presented a clinico-pathologic conference with a clinical discussion by Dr. Oscar Blitz. Dr. Guy Caldwell spoke on Correction of Discrepancies in Leg Lengths. Dr. Howard Karr discussed Diagnostic Use of Pantapaque.

GARDINER APPOINTED SUPERINTENDENT OF LAKESHORE HOSPITAL

It has been announced by the New Orleans Medical Foundation, the president of which is Dr. C. B. Odom, that Dr. W. P. Gardiner has been made superintendent of the Lakeshore Hospital. Dr. Gardiner has just completed a five year tour of duty in the Navy. He is a graduate of Tulane University School of Medicine where he obtained high scholastic honors as shown by being selected as a member of the honorary scholastic fraternity, Alpha Omega Alpha.

ROOT VISITS NEW ORLEANS

Dr. Howard F. Root, distinguished author, professor of Medicine at Harvard University, and authority on the management of Diabetic surgery at the Elliot P. Joslin Clinic in Boston, visited New Orleans as the guest of Dr. Robert A. Katz of Touro Infirmary and also of Captain E. H. Carnes and O. W. Williams of the U. S. Marine Hospital.

Dr. Root came to observe the original clinical work done here with diethyl ether in the treatment of impending gangrene. The U. S. Marine Hospital presented a program covering their experience with diethyl ether in 27 cases of peripheral disease. A demonstration of the use of atomic sodium in the measurement of circulatory improvement was also made.

MEDICAL REVIEW COURSES AT TULANE

Dr. Hiram W. Kostmayer, Director of the Division of Graduate Studies at Tulane, has announced a series of short review courses which will be held during the coming spring. Courses already have been conducted in gynecology and obstetrics, gastrointestinal diseases, and pulmonary diseases. On February 3-8, courses will be held in cardiovascular diseases; March 3-7, pediatrics; March 10-15, urinary diseases; March 17-22, nervous system diseases; March 24-29, nutritional and metabolic diseases; March 31-April 5, infectious diseases and April 7-12, neoplastic diseases. These courses will be conducted for the most part by members of the Tulane Medical School faculty, but for each course outside lecturers who are interested and prominent in the field will assist in the holding of the course.

NEWS ITEMS

Dr. Owen Wangensteen, Chief of the Department of Surgery and Professor of Surgery, The Medical School, University of Minnesota, lectured to the Fellows of the Alton Ochsner Medical Foundation on January 23, 1947 at 8:30 p. m. His subject was "The Problem of Gastric Ulcer".

In response to many inquiries from the public in reference to the use of glycols and ultraviolet radiation in control of airborne infections the National Institute of Health points out that the methods of controlling airborne infections are still within the experimental stage and no decision can be made as yet whether these methods are of value. Actually unshielded ultraviolet radiation is harmfull to the eyes and to the exposed skin of humans.

Through the cooperation of Mead Johnson & Company $34,000 in War Bonds are being offered to physician-artists (both in civilian and in military service) for best art works by physicians in war and in peace.

This contest is open to members of the American

Physicians Art Association and will be judged June 9-13, 1947 at the Atlantic City Session of the American Medical Association. For full details, write Dr. F. H. Redewill, Secretary, Flood Building, San Francisco, Cal., or Mead Johnson & Co., Evansville 21, Indiana.

Mr. Paul W. Roeder of Ciba Pharmaceutical Products, Inc., Summit, New Jersey, is very much concerned regarding the error in the slide rule they distributed to practically all of the physicians in the United States and have asked that this be called to the attention of our readers.

GROWTH OF LOUISIANA PHYSICIANS SERVICE
THE "BLUE SHIELD" PLAN

A report on the growth of Louisiana Physicians Service, Inc., is encouraging. In the first two months of active operation the company has been able to enroll 1,970 subscribers with 4,002 dependents making an aggregate of 5,972 individuals covered by the doctor's "Blue Shield" plan.

It is also encouraging to note the number of participating physicians who have voluntarily enrolled as participants in the plan. At the end of the year 517 physicians signed participating physicians agreements and as this story is going to press nearly 550 have enrolled to accept the fee schedule as contained in the policy certificate for surgical procedures as full payment for services rendered to members of the low income group, namely single individuals whose annual income is $2,000 or less and the family group whose aggregate family income is less than $3,000. Physicians participation in the plan is nearly 35% and it is hoped within a short time approximately 80% or 90% will see fit to enroll as participating members.

The company has been able to build in its two active months of enrollment an aggregate annual premium value in excess of $41,000.00. During this period it paid 13 claims submitted by the doctors and in each instance the claims were paid within a few days. This is another feature about the plan. The doctor only has to obtain the assignment of the policy certificate from the patient and then collect the amount stipulated in the Schedule of Benefits direct from the company without any red tape.

All expenses of management of the new company have been absorbed in its operation and nearly all of the preliminary expenses of organization have been absorbed in the first two months of operation.

There are still some physicians who are not familiar with the operation of the plan; however, it has been completely covered and explained in recent issues of the Journal.

At this time some might be asking. What is a prepayment surgical and obstetrical care plan? The answer is very simple. It is merely an organization that enrolls the subscribers, collects the assessment fees, and pays the benefits to the doctors for service rendered. Again these questions might be asked.

Are pre-payment surgical and obstetrical care plans in the public interest?

Are these plans good for our patients?

Are these plans good for the medical profession?

The answer to these questions is YES.

Louisiana Physicians Service, Inc., operates in the State of Louisiana and is sponsored and approved by the Louisiana State Medical Society. This plan has been granted the Seal of Acceptance of the Council on Medical Service of the American Medical Association. The plan has also been granted membership in Associated Medical Care Plans, the national organization of all pre-payment medical care plans.

From time to time you might hear the phrase "BLUE SHIELD". When a person refers to the "Blue Shield" plan he means the doctor's plan, for we bear the identification of the "Blue Shield". "Blue Shield" on a national basis means the organization of medical care plans to provide for the payment of the doctor's bill.

ASSOCIATION OF AMERICAN PHYSICIANS AND SURGEONS

On February 1, 1947, AAPS will launch its first Annual Essay Contest for Junior and Senior High School Students on the subject, "Why the Private Practice of Medicine Furnishes This Country With the Finest Medical Care."

The Association is offering $1,000 first prize; $500 second prize; and $100 third prize for the three best essays in the nation.

Essays must be limited to 1500 words and the Contest is open to Junior and Senior High School students of all schools, except sons and daughters of physicians.

Your Parish Medical Society is urged to sponsor a local contest and offer local prizes for the three best essays in your Parish. In the event your State Medical Society sponsors a state contest, the three winning essays in your Parish should be forwarded to State headquarters to compete for state prizes, with the three best essays in the State being sent on to the AAPS National Headquarters for participation in the National Contest. However, if your State Society does not sponsor a State Contest, send the three winning essays from your Parish directly to the Headquarters of the Association of American Physicians and Surgeons at 11 South LaSalle, Chicago 3, Illinois, for entry in the National Contest which ends March 30.

Medical leaders throughout the country believe that the AAPS Annual Essay Contest will constitute the most important contribution ever made to good public relations of organized medicine. Par-

ticipation in the Contest will require high school boys and girls to do research to become familiar with the reasons why the private practice of medicine provides this country with the finest medical care in the world. The contest affords medicine the opportunity of having its true and praiseworthy story reach the youngsters of all levels of population, and through them, their parents and teachers. Further, the Contest provides the means for medicine to dig deep in the grass roots of public opinion with the factual narrative of its accomplishments in the public interest.

FELLOWSHIPS FOR PHYSICIANS AND ENGINEERS

Announcement is made by Surgeon General Thomas Parran of the U. S. Public Health Service that applications for Fellowships in post-graduate public health training for physicians and engineers for the school year beginning in the fall of 1947 will be received at any time prior to May 1, 1947.

The Fellowships are made possible by a grant of $228,400 from the National Foundation for Infantile Paralysis through funds contributed to its March of Dimes. Fifty-three students were awarded Fellowships for the school year beginning in September 1946.

The specific purpose of the Fellowships is to aid in the recruitment of trained health officers, directors of special services, and engineers to help fill hundreds of vacancies existing in State and local health departments throughout the country. The Fellowships are intended for newcomers to the public health field, and are not open to employees of State and local health departments, for whom Federal grant-in-aid funds are already available to the States.

Applicants for Fellowships may secure further details by writing to the Surgeon General, U. S. Public Health Service, 19th and Constitution Avenue, N. W., Washington 25, D. C., Attention Public Health Training.

U. S. P. H. S. EXAMINATIONS

Competitive examinations will be held early in 1947 for appointment to the Regular Corps of the United States Public Health Service, according to a recent announcement by Dr. Thomas Parran, Surgeon General. Seventy-five vacancies exist in grades of Assistant and Senior Assistant Scientist.

Written examinations, covering each candidate's particular field of science, as well as related fields, will be held April 14 and 15 at places mutually convenient to the applicant and the Service. Oral examinations will be held during the period February 13-April 9 in thirty cities, strategically located throughout the United States; New Orleans, February 14.

Application forms and additional information may be obtained by writing the Surgeon General, United States Public Health Service, Washington 25, D. C.

PHYSICIANS WANTED

A physician qualified to do general practice, including obstetrics, is needed by the Myles Salt Company at Weeks, Louisiana. Equipped office furnished.

For further information contact Mr. Robert H. Polack, Vice-President, Post Office Box 329, New Orleans 9.

The office of the State Society has received information that there is need for a physician in Buras, Louisiana. Office space consisting of three rooms, including a small laboratory equipped with gas jet, work table, desk and running water is available.

If interested contact Mr. Peter C. LaDart, LaDart's Pharmacy, Buras, Louisiana. Telephone 2431.

HEALTH IN NEW ORLEANS

The Bureau of the Census, Department of Commerce, reported that for the week ending December 7 there were 130 deaths in the city of New Orleans as contrasted with 149 the previous week and 160 for the 3-year-average corresponding week. These deaths were divided as follows: white 93, non-white 37; 12 of the deaths occurred in children under one year of age. For the week which came to a close on December 14, there were 14 more deaths reported in the city of New Orleans than in the previous week. These were apportioned 91 white, 53 colored and 17 infants, most of whom were negro children. There were approximately the same number of deaths in the city for the week ending December 21 as the previous week, 146 versus 144. Of the total number of deaths, 99 occurred in the white population, 47 in the negro, with only seven infant deaths in this particular week. For some reason or another there was a sharp increase in the number of people dying in the city for the week ending December 28 as contrasted with the previous week. However, the number of deaths was still considerably smaller than the 3-year average; 102 of the white population died in the week closing December 28, 70 negroes expired and there were 11 infant deaths.

INFECTIOUS DISEASES IN LOUISIANA

The weekly morbidity report for the State of Louisiana for the week ending December 14 showed the following reportable diseases in numbers greater than ten; 25 cases of pulmonary tuberculosis, 20 of hookworm infestation and 13 of cancer. This is really quite a remarkable health record. There were three cases of poliomyelitis reported from

three different parishes and two cases of typhus fever. For the week which ended December 21, pulmonary tuberculosis led all reportable diseases with 61 cases followed by 21 of cancer, 27 of unclassified pneumonia, 14 of hookworm infestation and 10 of lobar pneumonia. The few cases of poliomyelitis, three, as were reported this week again, had their origin in three different parishes of the state. Probably the most unusual weekly morbidity report that has come to the Journal Office in many years was that of December 28 when the 43 cases of influenza which were listed represented the only reportable disease that occurred in frequency greater than eight. It may be that the Christmas season had a salubrious effect on the health of the Louisiana people or it may be that the Christmas cheer postponed the reporting of reportable cases.

MONTHLY MORBIDITY FOR VENEREAL DISEASES, STATE OF LOUISIANA

Month Ending November 30, 1946

	Total This Month	Total Previous Months	Total To Date 1946
Chancroid	39	556	595
Gonorrhea	1239	15756	16995
Granuloma Inguinale	28	252	280
Lymphopathia Venereum	2	97	99
Syphilis	1290	16960	18250

J. CYRIL EBY

1884-1946

Dr. Eby died suddenly of coronary occlusion in New Orleans while doing Christmas shopping. Dr. Eby was a graduate of the Maryland College of Pharmacy of the University of Maryland, 1916. He served during the first World War and then moved to Plaquemine in 1920. He soon became connected with the State Health Department and at the time of his death was the Iberville Parish Health Officer, serving also during the last war on account of the shortage of health officers in Ascension Parish.

WOMAN'S AUXILIARY

HIGHLIGHTS AND PROGRESS NOTES ON THE NATIONAL CONFERENCE OF PRESIDENTS AND PRESIDENTS-ELECT

The first joint meeting of the Board of Trustees of American Medical Association and the Board of the Woman's Auxiliary has taken place! It means that for the first time in the twenty-five years of its existence the Woman's Auxiliary has really come into its own and been recognized as a powerful asset to the A. M. A. A definite program of action for the Auxiliary will be formulated. Time and again, throughout most of the speeches by the doctors who spoke to the Conference it was brought out that the greatest challenge to doctors' wives was in the field of public relations. The task of educating the public to the aims and accomplishments of the medical profession, and teaching the desirability of the wide-spread use of voluntary medical insurance is one of the greatest services that the women of the Auxiliary can perform. But two points were stressed in this connection: *First*, that the best public relations were those which were the least obvious. Don't label open meetings as "Public Relations teas". Public relations is "just making friends",—and exhibiting a real interest in local problems and community welfare is the best way to cement finer Public Relations. *Secondly*, we must alter our attitude. We must *not* say the Voluntary Prepayment Plans are "our only weapon for fighting socialized medicine". Voluntary Prepayment Plans were designed, not to defeat the Wagner-Murray-Dingle bill, but to give *better* medical care to *more* people. The quality of medicine is above reproach; only the distribution is lacking.

Most state Auxiliaries now have study groups in which auxiliary members are learning about their local Voluntary Prepayment Plans, so that they can talk intelligently to lay persons.

Most states now hold annual Schools of Instruction for incoming officers and chairmen to familiarize them with their new duties. Louisiana plans to hold one at the Post Convention Board meeting.

Many states now have a mid-year conference of Presidents and Presidents-Elect patterned on Nationals, with round-table discussions. Louisiana approaches this plan in the mid-year Executive Board meeting.

Louisiana is the first state to hold state-wide open public relations meetings with a speaker to expose the dangers inherent in socialized medicine such as that proposed in the Wagner-Murray-Dingle bill. Mrs. Rex Fortenberry, a lawyer from Beaumont, Texas, has completed a tour of the entire state, speaking in all eight districts and contacting between 3,000 and 3,500 people.

Louisiana is the first state to ask the cooperation of the Auxiliary in aiding in the Survey of the American Academy of Pediatrics which is now being conducted on a national scale. And from reports of our local state chairman, Dr. C. H. Webb, the results of the Auxiliary's efforts in Louisiana are very gratifying. Louisiana's returns on the survey of general practitioners are 15.6 per cent higher than the pilot surveys!

Louisiana is now one of three states to publish an outline of its annual program. The other two are California and New York. Numerous requests for copies of the outline have been received from other states.

Several states have found that a membership file that lists all Auxiliary offices and activities of a member, as well as other club affiliations, to be

an invaluable asset to the state officers and nominating committee in choosing officer material. The national treasurer also asked that state treasurers be retained for more than one year, if possible.

It was also suggested that Public Relations chairmen urge that an up-to-date public relations file be kept on all local civic leaders of lay groups for facilitating speedy contacts with the proper persons to organize open meetings, health education programs, etc.

Debating kits are prepared and distributed to high schools, colleges and public libraries by many state auxiliaries. The Committee of Medical Services is prepared to furnish reference materials for these kits on Voluntary Prepayment Plans vs. Compulsory Insurance.

The Bureau of Health Education has two new members, Dr. Smiley of Cornell and Dr. Fred Hime, Ph. D. of Wisconsin, whose services as public speakers are available at A. M. A. expense to all states. They are expert consultants in the educational field.

Dr. W. W. Bauer, Director of Bureau of Health Education, also urged the wider use of electrical radio transcripts. There are fourteen series of platters on a variety of medical subjects now available together with the posters, press releases and necessary publicity, to furnish a fifteen minute program once a week for thirteen weeks, free of charge. Since program directors of local radio stations are required by law to make a report every three years on the amount of time *given* to public service projects they are usually more than glad to cooperate with any worthwhile organization.

Dr. Morris Fishbein reviewed the extensive plans being made for the celebration of the A. M. A.'s 100th anniversary at the Centennial Convention to be held in Atlantic City next June. A varied and imposing array of personalities and talent is being assembled for this meeting including such noted figures as Dr. Conant of Harvard, Kettering of General Electric, Monsignor Fulton Sheenan, Frank Howe Richardson, Zimbalist, Fred Waring and Guy Lombardo. There will be a March of Time recording the evolution and progress in the realm of medical science; the Postmaster General will probably endorse the issue of a special stamp commemorating the event; a history of the A. M. A. and the Medical Auxiliary is being prepared; and over 25,000 are expected to attend the largest convention ever held. I hope to see you in Atlantic City. (Further details will be printed in the next issue of the Journal.)

BOOK REVIEWS

Skin Diseases; Nutrition and Metabolism: By Erich Urbach, M.D., F.A.C.A., New York, Grune & Stratton, 1946. Illus. 634 p. Price, $10.00.

This new book contains a description of the metabolism and biochemistry of the skin, detailing the water, mineral, carbohydrates, lipid and protein metabolism of the skin with charts, reference to studies and experiments which clarify many of the modern theories of the skin's action. To the student who wants in a small chapter a concise knowledge of skin metabolism, a reader could not find the same amount of material in a whole volume.

The chapter on the Influence on Diet on Metabolism of the Skin, probably over-estimates the effect of diet on many diseases. The European idea of the beneficial effect of the Gerson and Sauerbruch-Hermannsdorfer diets is fully lauded but should be of great interest to younger students who have not acquainted themselves with the literature of the last generation. In part II of this volume the author discusses nutritional causes of dermatoses, listing those due to malnutrition, vitamin deficiencies, food allergies and alimentary infections and alimentary intoxications.

Allergy is discussed, described and many suggestions are given for the treatment of many skin diseases considered by the author to be of nutritional origin. The student of skin diseases, internal medicine, allergy and pediatrics should find this book a store house on the chemistry, physiology and metabolism of nutrition of the skin in health and disease.

M. T. VAN STUDDIFORD, M. D.

Synopsis of Genitourinary Diseases: By A. J. Dodson, M. D., F. A. C. S. 4th ed. St. Louis, C. V. Moshy Co., 1945. Pp. 313, illus. Price, $3.50.

This excellent book was designed to present a synopsis of genitourinary diseases, which could be easily assimilated by medical students, and to serve as a handy reference for the general practitioner. Etiology, pathology and diagnosis are stressed. Treatments are recommended, but the technics of procedures are necessarily omitted in this small edition.

The fourth edition includes a more comprehensive discussion of the uses and toxicity of the sulfonamide drugs, the use of penicillin and its application, a listing of bacteria which may be responsible for urinary tract infections, and the value of castration and endocrine therapy in the treatment of carcinoma of the prostate. The use of streptomycin is not included.

This book has admirably fulfilled the aims of its author, and is recommended to medical students, general practitioners and all physicians interested in urology.

JOHN G. MENVILLE, M. D.

Women in Industry: Their Health and Efficiency: By Anna M. Baetjer, Sc. D. Philadelphia and London: W. B. Saunders Co., 1946. 122 tales and 4 appendices, pp. 344. Price $4.00.

This study, begun during the war and carried out in the Army Industrial Hygiene Laboratory, is an exacting analysis of an exhaustive review of the literature on the question of utilization of womanpower in industry. Dr. Baetjer, throughout the book, made no attempt to justify the employment of women in any type of industrial work, either new or old to them, but did devote herself toward (1) making available any information that might be of value in proper placement of women when their service might be required in industry, (2) making an evaluation of any occupational effects on the physiologic processes in women, and (3) offering practical recommendations for industry in dealing with these problems.

The text is presented under six discussions of study: the ability of women to work, sickness absenteeism among women employees, accidental injuries to working women, occupational diseases, gynecologic and obstetrical problems associated with the employment of women, and mortality and fertility of women in relation to occupation. One hundred and twenty-two carefully planned tables are used. Four extensive appendices, an exhaustive 23-page bibliography, and a satisfactory index round out the book.

This volume will be of very definite interest as a handbook for industrial physicians and personnel managers as well as for members of industrial relations groups.

RALPH H. HEEREN, M. D.

The Venereal Diseases: By James Marshall, M. B., B. S., M. R. C. S., L. R. C. London, Macmillan & Co. Ltd., 1944. Pp. 348.

The author has succeeded in writing a general review of the diagnosis and treatment of venereal diseases, which should prove very helpful to general practitioners and students.

The book is divided into four parts, namely, gonorrhea, part I; syphilis, part II; other venereal and allied diseases, part III, and technic, part IV.

In part I, a short practical description of the anatomy of the genital organs of both sexes, the symptoms and signs of the disease, diagnostic procedures and the treatment of gonorrhea and its complications in the male and female are presented. Aspects of gonorrhea in both sexes, vulvovaginitis in children, urethral stricture and sulfonamides are discussed. Unfortunately, penicillin was in the experimental stage and all of the sulfonamides were not available in sufficient quantities when the book was written. This explains the space devoted to sulfapyridine in the treatment of gonorrhea.

In part II, syphilis, its complications and treatment, are covered in a well organized manner. The stages of the disease and its complications are extremely well illustrated and are invaluale to the student of this disease. The discussion of the drugs and the suggested courses of treatment are well outlined, efficient and comprehensible. Penicillin unfortunately is not included in the proposed treatments.

In part III, other venereal and allied diseases are discussed and a short practical synopsis of each is given.

In part IV, technic and practical instructions are covered and are valuable aids to all not versed in the common urological procedures.

The book is comprehensive, extremely well illustrated, well organized and practical. It should be a valuable guide to the general practitioner and student. Experience with penicillin and the commoner sulfonamides are not included.

JOHN G. MENVILLE, M. D.

New and Nonofficial Remedies, 1946, containing descriptions of the articles which stand accepted by the Council on Pharmacy and Chemistry of the American Medical Association on Jan. 1, 1946. Chicago, American Medical Association, 1946. Pp. 770. Cloth. Price, postpaid, $1.50.

New and Nonofficial Remedies is the book in which are listed and described the medicinal preparations which the Council on Pharmacy and Chemistry has found acceptable, under its rules, for the use of physicians. To have a product accepted, the manufacturer must declare its composition, give adequate proof of its therapeutic value and market it with claims which have been found valid by the Council. The present volume represents a cumulative epitome of the Council's work since its foundation in 1905.

Accepted preparations are grouped in twenty-four classifications ranging from allergenic preparations to vitamins. Ordinarily, an inclusive general article precedes the description of the various products. The monograph for the products set forth the actions, uses and dosage and usually a set of tests and standards. As its name implies, the book is intended to describe nonofficial preparations, that is preparations which are not included in such official publications as the Pharmacopeia and the National Formulary. However, some official articles are listed and described, these being in general those for which the Council feels the practicing physician needs concise and authoritative information. In the preface of the present volume, the Council lists some thirty-five official drugs ranging from acetylsalicylic acid to strophanthin, which the Council feels it no longer necessary to consider for inclusion in the book. However, in most cases, a brief monograph on actions, uses and dosage gives information useful to

the physician and for the control and advertising of marketed preparations.

Examination of the volume reveals that there have been no extensive or radical revisions of the general articles representing the twenty-four chapter heads under which preparations are classified. A few revisions of separate monographs may be mentioned: under chaulmoogra derivatives, the recommended use of chaulmoogra oil is limited to sarcoidosis; the dosage statement for quinacrine hydrochloride has been notably expanded to reflect the war-time experience with the drug. The radically revised monograph on amphetamine is in harmony with the recent Council report on the use of this drug. Minor revisions of the chapter on contraceptives are noted, and one marks the appearance of many additional products. The monograph on the vitamin B complex now mentions synthetic folic acid, recently made available for investigational use; but no accepted preparations are listed.

There appear to be no spectacularly new accepted preparations. Perhaps the most noteworthy is the casein hydrolysate, amigen, acceptance of which will no doubt be followed by that of many more preparations representing the field of amino acid therapy.

Diabetes—A Concise Presentation: By Henry J. John, M. A., M. D., F. A. C. P. St. Louis, The C. V. Mosby Company, 1946. Pp. 300. Price $3.25.

This is a rather unusual type of treatise on diabetes mellitus and seems to consist of a series of essays on various features of diabetes, not a concerted discourse on the disease itself. Thus there is no presentation at all of the relationships of diabetes and peripheral vascular disease, ocular disorders, various types of infectious diseases, of cardiac disease or any detailed discussion of the forms of insulin available today.

Dr. John is firmly convinced that hyperglycemia must not be neglected ("A continued hyperglycemia destroys a pancreas in time") one day after the diagnosis has been established, although many authorities will not agree with his contention. He believes that examination of the urine four times a day, as is so commonly practiced, is a very poor means of controlling the severity of the diabetes; he insists on a daily 24 hour estimation of urinary output of glucose and determination of the blood sugar levels three or four times a day while the patient is first under observation.

One chapter entitled "Some 'Do's' And 'Don'ts'" is given over to some detailed bits of advice reflecting the author's philosophic views on the treatment of patients in general and diabetics in particular. It comprises a range of topics from the psychologic approach to the patient to suggestions for performing venipuncture.

SYDNEY JACOBS, M. D.

The Modern Treatment of Diabetes Mellitus: By William S. Collens, B. S., M. D., and Louis C. Boas, A. B., M. D. Springfield, Illinois, Charles C. Thomas, 1946. Pp. 514. Price $8.50.

This is a good treatise on diabetes mellitus and fulfills its purpose of acting as "a practical comprehensive guide for the general practitioners who treat diabetic patients". In line with the current tendency to simplify the treatment of diabetes mellitus, the tone of the book is almost dogmatic at times.

The historical introduction is unusually well-written and informative. The conventional presentation of allotting a chapter to each of the important considerations of diabetes is carried to the logical extreme of a therapeutic classification. Thus according to the severity of the illness, certain differing modes of therapy are given. Although this makes for some repetition, the result is good. In all chapters, the attempt is made to present to the clinician a maximum of applicable data and a minimum of "theoretical" background.

Several features deserve comment. The chapter on vascular diseases is exceptionally good; the use of illustrations in color materially improves the presentation. In view of the long interest of both authors in peripheral vascular disease, this is not remarkable. The direct and pointed suggestions for the solution of problems of vascular disease (either peripherally or of the coronary system) is most valuable. For an unexplained reason, the relationship of high fat diets to the incitement and aggravation of peripheral vascular disease is not included.

The use of "clock" diagrams to point out the effects of modified and of unmodified insulins during a 24 hour period is helpful in deciding which form of insulin to use under a given set of circumstances. The liberal use of photographs, charts and sketches is additionally illustrative. Important points are placed in italics or in bold face type, thus compelling attention.

The chapter on diabetes of the pregnant woman is rather scantily presented, and the hormonal approach to prevention and therapy of the toxemias is not critically stated. Sterility of the diabetic, the use of estrogenic substances to modify the diabetes of middle-aged females, the occurrence of hemochromatosis and the co-existence of tuberculosis and diabetes are not mentioned in the book.

Despite these deficiencies, it is to be recommended to anyone wishing a practical method of handling the more frequent diabetic problem.

SYDNEY JACOBS, M. D.

Progress in Neurology and Psychiatry: Ed. by E. A. Spiegel. New York, Grune & Stratton, 1946. Pp. 708. Price, $8.00.

Increased interest in neuropsychiatric problems has been responsible for many valuable treatises on these subjects. This volume has the distinction

of being the first of a series of annual reviews which are not intended to replace existing abstract services but they will attempt to supplement them by providing critical surveys of the basic theoretical foundations as well as of various clinical aspects of neurology and psychiatry.

Edited by Doctor E. A. Spiegel, a distinguished scientist and investigator and a prodigious worker in the field of neuropsychiatry, this work includes some thirty-five contributions by an equal number of eminent specialists. Each chapter adequately surveys its special subject. All sections are splendidly done and those chapters on Psychoanalysis, Group Psychotherapy and the parts dealing with tics and management of speech disorders, are excellent.

The book as a whole is an up-to-the-present refresher course which brings one all the important advances. It is a comprehensive readable review which might be added to every physician's library and used with profit.

C. P. MAY, M. D.

Harvey Cushing, a Biography: By John F. Fulton, Springfield, Ill., Charles C. Thomas, 1946. Por. pp. 754. Illus. Price, $5.00.

The story of Harvey Cushing (1869-1939) by his literary executor, the eminent Dr. John F. Fulton, may not appeal to those who have acquired a taste for fictionized biography. Other biographers and students of medical history, and of character, undoubtedly will commend the meticulous method by which are recorded the life events of a master surgeon and man of letters. Considerable time will be required for careful reading of the more than 750 pages of text, the greater portion of which is composed in eight and nine point type, but there is rich reward to be gained in following the mental and spiritual development of the extraordinary individual whose portrait is honestly and understandingly presented.

Anticipating that an account of his life might be "of interest or help to medical students," Cushing provided funds for compiling this volume from which royalties will be paid to the Medical Historical Library of Yale University. Dr. Fulton accepted his difficult assignment in much the same spirit that inspired Cushing to write his imperishable *Life of Sir William Osler*, the Pulitzer prize-biography of 1925. With selective judgment he has chosen from an abundance of source material concerning the external life of his friend who became the leading neurological surgeon in the world. Interwoven are many illuminating incidents in the lives of heroic medical men — Osler, Halsted, Welch, Klebs, Kelly, Finney, Sherrington, John Homans and others with whom he was associated. Of no less interest are the accounts of his associations with the great medical institutions of Yale, Harvard, John Hopkins, Massachusetts General, and Peter Bent Brigham hospitals.

Throughout the voluminous correspondence that is included are intimate glimpses of the inner man which enlarge our understanding of his complicated character. Diaries from student days, descriptions of travels illustrated by his facile pencil, cuttings from files and scrapbooks, letters to his family which had been carefully preserved by his father — in these does one discover Cushing's great love of nature, his pride in his illustrious forebears, his strong family ties and devotion to his physician-brother "Ned," his interest in his patients and their families, his concern with needy students, wartime experiences, occasional conflicts, his professional attainments, honors and recognition — one can only suggest the wealth of material that is revealed in this sharp and clear delineation of a great and a useful life. Throughout each chapter the reader is ever conscious of the motivating force that enabled Cushing to succeed in varied fields of endeavor, of his driving ambition to attain perfection and his almost fanatical passion for work to which his life was devoted even through periods of physical weakness.

In our opinion, the book succeeds in what has been termed the "most delicate and humane of all forms of writing" and will serve as an inspiring example for students, holding interest for all who are concerned with the problems of medical education and of practice. Dr. Fulton has made an enduring contribution in his historic volume from which we quote the closing words: " 'By valor and divine aid,' he (Cushing) had more than fulfilled the promise and ambition of his youth: scientist, pathfinder, artist, writer, and bibliophile — yes, and above all, 'a good doctor'."

DEAN H. ECHOLS, M. D.

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